```
=> d his full

     (FILE 'HOME' ENTERED AT 09:30:05 ON 11 OCT 2007)

     FILE 'REGISTRY' ENTERED AT 09:30:15 ON 11 OCT 2007
L1                STRUCTURE UPLOADED
L2              1 SEA SSS SAM L1
                  D SCA
L3            560 SEA SSS FUL L1
                  SAVE TEMP L3 LAO058STR1L/A

     FILE 'ZCAPLUS' ENTERED AT 09:35:51 ON 11 OCT 2007
L4            117 SEA ABB=ON  PLU=ON  L3
L5                ANALYZE PLU=ON  L4 1- RN :    5098 TERMS
                  D
                  D
                  D 1-20

     FILE 'REGISTRY' ENTERED AT 09:37:09 ON 11 OCT 2007
L6              1 SEA ABB=ON  PLU=ON  152044-54-7
L7              1 SEA ABB=ON  PLU=ON  152044-53-6
L8              1 SEA ABB=ON  PLU=ON  189453-10-9
L9              1 SEA ABB=ON  PLU=ON  186692-73-9
L10             1 SEA ABB=ON  PLU=ON  187527-25-9
L11             1 SEA ABB=ON  PLU=ON  188730-08-7
L12             1 SEA ABB=ON  PLU=ON  20949-84-2
L13             1 SEA ABB=ON  PLU=ON  106921-60-2
L14             1 SEA ABB=ON  PLU=ON  193146-27-9
L15             0 SEA ABB=ON  PLU=ON  (L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12
                  OR L13 OR L14) AND L4
L16             0 SEA ABB=ON  PLU=ON  (L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12
                  OR L13 OR L14) AND L3
L17             1 SEA ABB=ON  PLU=ON  187283-46-1
L18             1 SEA ABB=ON  PLU=ON  188899-14-1
L*** DEL        0 S S 184246-38-6
L19             1 SEA ABB=ON  PLU=ON  184246-38-6
L20             1 SEA ABB=ON  PLU=ON  189453-35-8
L21             1 SEA ABB=ON  PLU=ON  219989-84-1
L22             1 SEA ABB=ON  PLU=ON  63928-37-0
L23             1 SEA ABB=ON  PLU=ON  52079-23-9
L24             1 SEA ABB=ON  PLU=ON  70113-32-5
L25             1 SEA ABB=ON  PLU=ON  185148-95-2
L26             1 SEA ABB=ON  PLU=ON  186692-84-2
L27             0 SEA ABB=ON  PLU=ON  L3 AND (L6 OR L7 OR L8 OR L9 OR L10 OR L11
                  OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20
                  OR L21 OR L22 OR L23 OR L24 OR L25 OR L26)
L28           191 SEA ABB=ON  PLU=ON  L3 AND CASREACT/LC

     FILE 'ZCAPLUS' ENTERED AT 09:43:45 ON 11 OCT 2007
L29           115 SEA ABB=ON  PLU=ON  L3/P

     FILE 'CASREACT' ENTERED AT 09:53:42 ON 11 OCT 2007
L30            69 SEA ABB=ON  PLU=ON  L3
L31                STRUCTURE UPLOADED
L32             0 SEA SUB=L30 SSS SAM L31 (     0 REACTIONS)
L33            23 SEA SUB=L30 SSS FUL L31 (   468 REACTIONS)
                  D STAT QUE L33
```

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     FILE 'REGISTRY' ENTERED AT 11:21:02 ON 11 OCT 2007
L34       22933 SEA ABB=ON  PLU=ON  OC15/ESS
L35       27330 SEA ABB=ON  PLU=ON  C16/ESS
L36         726 SEA ABB=ON  PLU=ON  NC15/ESS
L37           0 SEA ABB=ON  PLU=ON  NSC14/ESS
L38       50989 SEA ABB=ON  PLU=ON  (L34 OR L35 OR L36 OR L37)
L39       12165 SEA ABB=ON  PLU=ON  L38 AND CASREACT/LC

     FILE 'CASREACT' ENTERED AT 11:22:32 ON 11 OCT 2007
L40        2534 SEA ABB=ON  PLU=ON  L39/PRO
L41          59 SEA ABB=ON  PLU=ON  L30 (L) L40
L42          65 SEA ABB=ON  PLU=ON  L3/RRT
L43          59 SEA ABB=ON  PLU=ON  L42 (L) L40
L44          19 SEA ABB=ON  PLU=ON  L43 AND L33

     FILE 'CAPLUS' ENTERED AT 11:34:47 ON 11 OCT 2007
L45          59 SEA ABB=ON  PLU=ON  L43
L46          53 SEA ABB=ON  PLU=ON  L45 AND PY<2005
L47          49 SEA ABB=ON  PLU=ON  L45 AND PY<2004

     FILE 'CASREACT' ENTERED AT 11:35:34 ON 11 OCT 2007
                D L43
L48          59 SEA ABB=ON  PLU=ON  L43 AND 1/NS
L49          50 SEA ABB=ON  PLU=ON  L43 AND 2/NS
L50          44 SEA ABB=ON  PLU=ON  L43 AND 3/NS
L51          42 SEA ABB=ON  PLU=ON  L43 AND 4/NS
L52           9 SEA ABB=ON  PLU=ON  L48 NOT L49
                D SCA

     FILE 'CAPLUS' ENTERED AT 11:45:06 ON 11 OCT 2007
L53          45 SEA ABB=ON  PLU=ON  L45 AND J/DT
L54          14 SEA ABB=ON  PLU=ON  L45 AND P/DT
L55          12 SEA ABB=ON  PLU=ON  L54 AND PD<20040619
L56          39 SEA ABB=ON  PLU=ON  L53 AND ED<20040619
L57           6 SEA ABB=ON  PLU=ON  L53 NOT L56
L58           2 SEA ABB=ON  PLU=ON  L54 NOT L55
L59           8 SEA ABB=ON  PLU=ON  (L57 OR L58)
                SEL AN

     FILE 'CASREACT' ENTERED AT 11:47:33 ON 11 OCT 2007
L60           8 SEA ABB=ON  PLU=ON  ("142:134344"/AN OR "143:211773"/AN OR
                "143:422202"/AN OR "144:170808"/AN OR "145:271524"/AN OR
                "145:397261"/AN OR "146:229070"/AN OR "146:251631"/AN OR
                "2004:985335"/AN OR "2005:1154536"/AN OR "2005:1305128"/AN OR
                "2005:614221"/AN OR "2006:1337456"/AN OR "2006:641138"/AN OR
                "2006:66747"/AN OR "2006:805502"/AN)
L61          51 SEA ABB=ON  PLU=ON  L48 NOT L60
L62          42 SEA ABB=ON  PLU=ON  L49 NOT L60
L63          36 SEA ABB=ON  PLU=ON  L50 NOT L60
L64          35 SEA ABB=ON  PLU=ON  L51 NOT L60

     FILE 'CAPLUS' ENTERED AT 11:49:27 ON 11 OCT 2007
                E US2006-563058 /APPS
L65           1 SEA ABB=ON  PLU=ON  US2006-563058 /AP
                D SCA
                SEL RN

     FILE 'REGISTRY' ENTERED AT 11:50:13 ON 11 OCT 2007
L66          55 SEA ABB=ON  PLU=ON  (130486-85-0/BI OR 152044-53-6/BI OR
                152044-54-7/BI OR 185148-95-2/BI OR 220367-73-7/BI OR 220774-16
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                -3/BI OR 220774-19-6/BI OR 220774-20-9/BI OR 220774-21-0/BI OR
                220774-22-1/BI OR 220774-23-2/BI OR 220774-57-2/BI OR 220774-58
                -3/BI OR 220774-59-4/BI OR 220774-60-7/BI OR 220774-61-8/BI OR
                220774-62-9/BI OR 220775-18-8/BI OR 220775-76-8/BI OR 289477-70
                -9/BI OR 289477-71-0/BI OR 289477-72-1/BI OR 289477-73-2/BI OR
                289477-74-3/BI OR 303154-55-4/BI OR 303154-56-5/BI OR 303154-57
                -6/BI OR 303154-58-7/BI OR 303154-59-8/BI OR 303154-60-1/BI OR
                305840-13-5/BI OR 823203-01-6/BI OR 823203-02-7/BI OR 823203-03
                -8/BI OR 823203-04-9/BI OR 823203-05-0/BI OR 823203-06-1/BI OR
                823203-07-2/BI OR 823203-08-3/BI OR 823203-09-4/BI OR 823203-10
                -7/BI OR 823203-11-8/BI OR 823203-12-9/BI OR 823203-13-0/BI OR
                823203-14-1/BI OR 823203-15-2/BI OR 823203-16-3/BI OR 823203-17
                -4/BI OR 823203-18-5/BI OR 823203-19-6/BI OR 823203-20-9/BI OR
                823203-23-2/BI OR 823203-24-3/BI OR 823203-25-4/BI OR 823203-27
                -6/BI)
L67           2 SEA ABB=ON  PLU=ON  L66 AND L39
                D SCA

     FILE 'CAPLUS' ENTERED AT 11:50:53 ON 11 OCT 2007
L68           1 SEA ABB=ON  PLU=ON  L67 AND L65
                D SCA

     FILE 'REGISTRY' ENTERED AT 11:54:40 ON 11 OCT 2007
                E EPOTHILONE C/CN
L69           1 SEA ABB=ON  PLU=ON  EPOTHILONE C/CN
                D SCA
L70           1 SEA ABB=ON  PLU=ON  EPOTHILONE D/CN
                D SCA
                D RN L67 1-2

     FILE 'CASREACT' ENTERED AT 11:56:56 ON 11 OCT 2007
L71          21 SEA ABB=ON  PLU=ON  152044-54-7/PRO
L72          14 SEA ABB=ON  PLU=ON  152044-53-6/PRO
L73           7 SEA ABB=ON  PLU=ON  L42 (L) L71
L74           7 SEA ABB=ON  PLU=ON  L42 (L) L72
L75          14 SEA ABB=ON  PLU=ON  (L73 OR L74)
L76          13 SEA ABB=ON  PLU=ON  L75 NOT L60

     FILE 'CAPLUS' ENTERED AT 11:58:45 ON 11 OCT 2007
L77          11 SEA ABB=ON  PLU=ON  L45 AND PY<2000
                SEL AN

     FILE 'CASREACT' ENTERED AT 12:00:01 ON 11 OCT 2007
L78          11 SEA ABB=ON  PLU=ON  ("126:251010"/AN OR "127:108793"/AN OR
                "127:293040"/AN OR "128:101936"/AN OR "129:189151"/AN OR
                "131:199535"/AN OR "131:286299"/AN OR "131:31819"/AN OR
                "131:31829"/AN OR "131:351125"/AN OR "132:49832"/AN OR
                "1997:206419"/AN OR "1997:430309"/AN OR "1997:665094"/AN OR
                "1997:787450"/AN OR "1998:378435"/AN OR "1999:176999"/AN OR
                "1999:372044"/AN OR "1999:383492"/AN OR "1999:444724"/AN OR
                "1999:606636"/AN OR "1999:819379"/AN)
L79          11 SEA ABB=ON  PLU=ON  L78 AND L43
L80          16 SEA ABB=ON  PLU=ON  L79 OR L52
L81           1 SEA ABB=ON  PLU=ON  L80 AND L73
L82           1 SEA ABB=ON  PLU=ON  L80 AND L74
L83          27 SEA ABB=ON  PLU=ON  L52 OR L79 OR (L81 OR L82) OR L76
L84          15 SEA ABB=ON  PLU=ON  L61 NOT L63
                D FHIT 7
L85          59 SEA ABB=ON  PLU=ON  L43 (L) 1/NS
L86          45 SEA ABB=ON  PLU=ON  L43 (L) 2/NS
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L87          37 SEA ABB=ON  PLU=ON  L43 (L) 3/NS
L88          31 SEA ABB=ON  PLU=ON  L43 (L) 4/NS
L89          21 SEA ABB=ON  PLU=ON  L43 (L) 5/NS
L90          28 SEA ABB=ON  PLU=ON  L85 NOT L88

     FILE 'CAPLUS' ENTERED AT 12:09:08 ON 11 OCT 2007
L91          80 SEA ABB=ON  PLU=ON  KLAR U?/AU
L92         116 SEA ABB=ON  PLU=ON  BUCHMANN B?/AU
L93          60 SEA ABB=ON  PLU=ON  SCHWEDE W?/AU
L94         186 SEA ABB=ON  PLU=ON  SKUBALLA W?/AU
L95          32 SEA ABB=ON  PLU=ON  L91 AND (L92 OR L93 OR L94)
L96          68 SEA ABB=ON  PLU=ON  L92 AND (L93 OR L94)
L97          24 SEA ABB=ON  PLU=ON  L93 AND L94
L98          25 SEA ABB=ON  PLU=ON  L95 AND (L96 OR L97)
L99          24 SEA ABB=ON  PLU=ON  L96 AND L97
L100         24 SEA ABB=ON  PLU=ON  L98 AND L99
L101          1 SEA ABB=ON  PLU=ON  L100 AND L43

     FILE 'REGISTRY' ENTERED AT 12:11:27 ON 11 OCT 2007

     FILE 'CAPLUS' ENTERED AT 12:11:29 ON 11 OCT 2007
               D STAT QUE L100
               D IBIB ABS L100 1-24
               D IBIB ABS L100 8-24
L102         24 SEA ABB=ON  PLU=ON  L91 AND L92 AND L93 AND L94
               D COST FULL
               D IBIB ABS L102 TOT
               D IBIB L102 10
               D IBIB L102 9
               D ABS L102 8
               D ABS L102 8
               D IBIB ABS L102 9-24

     FILE 'REGISTRY' ENTERED AT 12:16:30 ON 11 OCT 2007

     FILE 'CASREACT' ENTERED AT 12:16:34 ON 11 OCT 2007
               D STAT QUE L33
               D IBIB ABS FHIT L33 1-23

     FILE 'CASREACT' ENTERED AT 12:18:14 ON 11 OCT 2007
               D STAT QUE L90
               D IBIB ABS FHIT L90 1-28
L103          3 SEA ABB=ON  PLU=ON  L77 NOT L90
L104          3 SEA ABB=ON  PLU=ON  L78 NOT L90

     FILE 'CAPLUS' ENTERED AT 12:40:57 ON 11 OCT 2007
L105         21 SEA ABB=ON  PLU=ON  L45 AND PY<2001
               SEL AN

     FILE 'CASREACT' ENTERED AT 12:41:26 ON 11 OCT 2007
L106         21 SEA ABB=ON  PLU=ON  ("126:251010"/AN OR "127:108793"/AN OR
               "127:293040"/AN OR "128:101936"/AN OR "129:189151"/AN OR
               "131:199535"/AN OR "131:286299"/AN OR "131:31819"/AN OR
               "131:31829"/AN OR "131:351125"/AN OR "132:251011"/AN OR
               "132:49832"/AN OR "133:266631"/AN OR "133:266634"/AN OR
               "133:321737"/AN OR "133:362657"/AN OR "134:178371"/AN OR
               "134:29228"/AN OR "134:4795"/AN OR "134:56502"/AN OR "135:37156
               6"/AN OR "1997:206419"/AN OR "1997:430309"/AN OR "1997:665094"/
               AN OR "1997:787450"/AN OR "1998:378435"/AN OR "1999:176999"/AN
               OR "1999:372044"/AN OR "1999:383492"/AN OR "1999:444724"/AN OR
```

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                "1999:606636"/AN OR "1999:819379"/AN OR "2000:514132"/AN OR
                "2000:52387"/AN OR "2000:597944"/AN OR "2000:624043"/AN OR
                "2000:701228"/AN OR "2000:719579"/AN OR "2000:733774"/AN OR
                "2000:842116"/AN OR "2000:853645"/AN OR "2001:843887"/AN)
L107          7 SEA ABB=ON  PLU=ON  L106 NOT L90
L108         21 SEA ABB=ON  PLU=ON  L106 AND L43
L109          7 SEA ABB=ON  PLU=ON  L108 NOT L90
                D STAT QUE L109
                D IBIB ABS FHIT L109 1-7
```

FILE HOME

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1
DICTIONARY FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

FILE ZCAPLUS

FILE COVERS 1907 - 11 Oct 2007 VOL 147 ISS 16
FILE LAST UPDATED: 10 Oct 2007 (20071010/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE CASREACT

FILE CONTENT:1840 - 6 Oct 2007 VOL 147 ISS 16

New CAS Information Use Policies, enter HELP USAGETERMS for details.

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**********************************************************
*                                                        *
*     CASREACT now has more than 13.8 million reactions  *
*                                                        *
**********************************************************
```

Some CASREACT records are derived from the ZIC/VINITI database (1974-1999) provided by InfoChem, INPI data prior to 1986, and Biotransformations database compiled under the direction of Professor Dr. Klaus Kieslich.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE CAPLUS

FILE COVERS 1907 - 11 Oct 2007 VOL 147 ISS 16
FILE LAST UPDATED: 10 Oct 2007 (20071010/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

http://www.cas.org/infopolicy.html

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=> d his full

     (FILE 'HOME' ENTERED AT 09:30:05 ON 11 OCT 2007)

     FILE 'REGISTRY' ENTERED AT 09:30:15 ON 11 OCT 2007
L1                STRUCTURE UPLOADED
L2              1 SEA SSS SAM L1
                  D SCA
L3            560 SEA SSS FUL L1
                  SAVE TEMP L3 LA0058STR1L/A

     FILE 'ZCAPLUS' ENTERED AT 09:35:51 ON 11 OCT 2007
L4            117 SEA ABB=ON  PLU=ON  L3
L5                ANALYZE PLU=ON  L4 1- RN :    5098 TERMS
                  D
                  D
                  D 1-20

     FILE 'REGISTRY' ENTERED AT 09:37:09 ON 11 OCT 2007
L6              1 SEA ABB=ON  PLU=ON  152044-54-7
L7              1 SEA ABB=ON  PLU=ON  152044-53-6
L8              1 SEA ABB=ON  PLU=ON  189453-10-9
L9              1 SEA ABB=ON  PLU=ON  186692-73-9
L10             1 SEA ABB=ON  PLU=ON  187527-25-9
L11             1 SEA ABB=ON  PLU=ON  188730-08-7
L12             1 SEA ABB=ON  PLU=ON  20949-84-2
L13             1 SEA ABB=ON  PLU=ON  106921-60-2
L14             1 SEA ABB=ON  PLU=ON  193146-27-9
L15             0 SEA ABB=ON  PLU=ON  (L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12
                  OR L13 OR L14) AND L4
L16             0 SEA ABB=ON  PLU=ON  (L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12
                  OR L13 OR L14) AND L3
L17             1 SEA ABB=ON  PLU=ON  187283-46-1
L18             1 SEA ABB=ON  PLU=ON  188899-14-1
L*** DEL        0 S S 184246-38-6
L19             1 SEA ABB=ON  PLU=ON  184246-38-6
L20             1 SEA ABB=ON  PLU=ON  189453-35-8
L21             1 SEA ABB=ON  PLU=ON  219989-84-1
L22             1 SEA ABB=ON  PLU=ON  63928-37-0
L23             1 SEA ABB=ON  PLU=ON  52079-23-9
L24             1 SEA ABB=ON  PLU=ON  70113-32-5
L25             1 SEA ABB=ON  PLU=ON  185148-95-2
L26             1 SEA ABB=ON  PLU=ON  186692-84-2
L27             0 SEA ABB=ON  PLU=ON  L3 AND (L6 OR L7 OR L8 OR L9 OR L10 OR L11
                  OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20
                  OR L21 OR L22 OR L23 OR L24 OR L25 OR L26)
L28           191 SEA ABB=ON  PLU=ON  L3 AND CASREACT/LC

     FILE 'ZCAPLUS' ENTERED AT 09:43:45 ON 11 OCT 2007
L29           115 SEA ABB=ON  PLU=ON  L3/P

     FILE 'CASREACT' ENTERED AT 09:53:42 ON 11 OCT 2007
L30            69 SEA ABB=ON  PLU=ON  L3
L31                STRUCTURE UPLOADED
L32             0 SEA SUB=L30 SSS SAM L31 (     0 REACTIONS)
L33            23 SEA SUB=L30 SSS FUL L31 (   468 REACTIONS)
                  D STAT QUE L33
```



```
     FILE 'REGISTRY' ENTERED AT 11:21:02 ON 11 OCT 2007
L34         22933 SEA ABB=ON  PLU=ON  OC15/ESS
L35         27330 SEA ABB=ON  PLU=ON  C16/ESS
L36           726 SEA ABB=ON  PLU=ON  NC15/ESS
L37             0 SEA ABB=ON  PLU=ON  NSC14/ESS
L38         50989 SEA ABB=ON  PLU=ON  (L34 OR L35 OR L36 OR L37)
L39         12165 SEA ABB=ON  PLU=ON  L38 AND CASREACT/LC

     FILE 'CASREACT' ENTERED AT 11:22:32 ON 11 OCT 2007
L40          2534 SEA ABB=ON  PLU=ON  L39/PRO
L41            59 SEA ABB=ON  PLU=ON  L30 (L) L40
L42            65 SEA ABB=ON  PLU=ON  L3/RRT
L43            59 SEA ABB=ON  PLU=ON  L42 (L) L40
L44            19 SEA ABB=ON  PLU=ON  L43 AND L33

     FILE 'CAPLUS' ENTERED AT 11:34:47 ON 11 OCT 2007
L45            59 SEA ABB=ON  PLU=ON  L43
L46            53 SEA ABB=ON  PLU=ON  L45 AND PY<2005
L47            49 SEA ABB=ON  PLU=ON  L45 AND PY<2004

     FILE 'CASREACT' ENTERED AT 11:35:34 ON 11 OCT 2007
                  D L43
L48            59 SEA ABB=ON  PLU=ON  L43 AND 1/NS
L49            50 SEA ABB=ON  PLU=ON  L43 AND 2/NS
L50            44 SEA ABB=ON  PLU=ON  L43 AND 3/NS
L51            42 SEA ABB=ON  PLU=ON  L43 AND 4/NS
L52             9 SEA ABB=ON  PLU=ON  L48 NOT L49
                  D SCA

     FILE 'CAPLUS' ENTERED AT 11:45:06 ON 11 OCT 2007
L53            45 SEA ABB=ON  PLU=ON  L45 AND J/DT
L54            14 SEA ABB=ON  PLU=ON  L45 AND P/DT
L55            12 SEA ABB=ON  PLU=ON  L54 AND PD<20040619
L56            39 SEA ABB=ON  PLU=ON  L53 AND ED<20040619
L57             6 SEA ABB=ON  PLU=ON  L53 NOT L56
L58             2 SEA ABB=ON  PLU=ON  L54 NOT L55
L59             8 SEA ABB=ON  PLU=ON  (L57 OR L58)
                  SEL AN

     FILE 'CASREACT' ENTERED AT 11:47:33 ON 11 OCT 2007
L60             8 SEA ABB=ON  PLU=ON  ("142:134344"/AN OR "143:211773"/AN OR
                  "143:422202"/AN OR "144:170808"/AN OR "145:271524"/AN OR
                  "145:397261"/AN OR "146:229070"/AN OR "146:251631"/AN OR
                  "2004:985335"/AN OR "2005:1154536"/AN OR "2005:1305128"/AN OR
                  "2005:614221"/AN OR "2006:1337456"/AN OR "2006:641138"/AN OR
                  "2006:66747"/AN OR "2006:805502"/AN)
L61            51 SEA ABB=ON  PLU=ON  L48 NOT L60
L62            42 SEA ABB=ON  PLU=ON  L49 NOT L60
L63            36 SEA ABB=ON  PLU=ON  L50 NOT L60
L64            35 SEA ABB=ON  PLU=ON  L51 NOT L60

     FILE 'CAPLUS' ENTERED AT 11:49:27 ON 11 OCT 2007
                  E US2006-563058 /APPS
L65             1 SEA ABB=ON  PLU=ON  US2006-563058 /AP
                  D SCA
                  SEL RN

     FILE 'REGISTRY' ENTERED AT 11:50:13 ON 11 OCT 2007
L66            55 SEA ABB=ON  PLU=ON  (130486-85-0/BI OR 152044-53-6/BI OR
                  152044-54-7/BI OR 185148-95-2/BI OR 220367-73-7/BI OR 220774-16
```

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(3) RCT H ***188730-19-0***

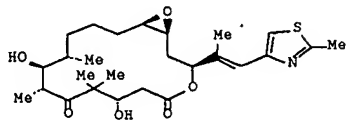
STAGE(1)
RGT J 4136-95-2 2,4,6-Cl3C6H2COCl, K 121-44-8 Et3N
SOL 109-99-9 THF

STAGE(2)
RGT L 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

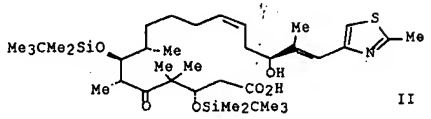
PRO I ***186692-84-2***
NTE key step

REFERENCE COUNT: 100 THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 28 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 126:251010 CASREACT Full-text
TITLE: Total synthesis of epothilone A: the macrolactonization approach
AUTHOR(S): Nicolaou, K. C.; Sarabia, Francisco; Ninkovic, Sacha; Yang, Zhen
CORPORATE SOURCE: Dep. Chem., Skaggs Inst. Chem. Biol., Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE: Angewandte Chemie, International Edition in English (1997), 36(5), 525-527
CODEN: ACIEAY; ISSN: 0570-0833
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



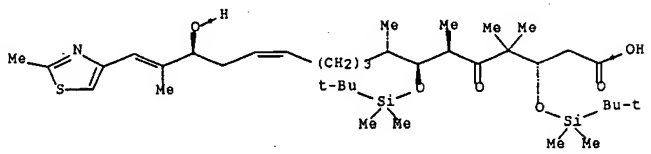
I



II

AB Epothilone A (I) was prepared via a highly convergent and flexible route with macrolactonization of hydroxy acid II as the key step.

RX(4) OF 4 ***M*** ===> ***N***



M

(4)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

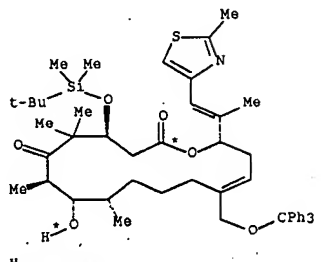
RX(4) RCT M ***188730-19-0***

STAGE(1)
RGT O 4136-95-2 2,4,6-Cl3C6H2COCl, P 121-44-8 Et3N
SOL 109-99-9 THF

STAGE(2)
RGT Q 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

PRO N ***186692-84-2***
NTE key step

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT



H
YIELD 75%

RX(2) RCT G *201136-77-8*

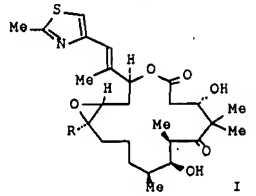
STAGE(1)
RGT I 4136-95-2 2,4,6-Cl3C6H2COCl, J 121-44-8 Et3N
SOL 109-99-9 THF

STAGE(2)
RGT K 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

PRO H *201136-78-9*

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

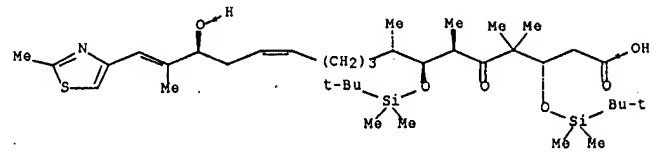
L90 ANSWER 27 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 127:293040 CASREACT Full-text
TITLE: Total Syntheses of Epothilones A and B
AUTHOR(S): Meng, Dongfang; Bertinato, Peter; Balog, Aaron; Su, Dai-Shi; Kamenecka, Ted; Sorensen, Erik; Danishefsky, Samuel J.
CORPORATE SOURCE: Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE: Journal of the American Chemical Society (1997), 119(42), 10073-10092
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Convergent, stereocontrolled total syntheses of the microtubule- stabilizing macrolides epothilones A (I; R = H) and B (I; R = Me) have been achieved. Four distinct ring-forming strategies were pursued. Of these four, three were reduced to practice. In one approach, the action of a base on a substance possessing an acetate ester and a nonenolizable aldehyde brought about a remarkably effective macroaldolization simultaneously creating the C2-C3 bond and the hydroxyl-bearing stereocenter at C-3. Alternatively, the 16-membered macrolide of the epothilones could be fashioned through a C12-C13 ring-closing olefin metathesis and through macrolactonization of the appropriate hydroxy acid. The application of a stereospecific B-alkyl Suzuki coupling strategy permitted the establishment of a cis C12-C13 olefin, thus setting the stage for an eventual site- and diastereoselective epoxidn. reaction. The development of a novel cyclopropane solvolysis strategy for incorporating the geminal Me groups of the epothilones, and the use of Lewis acid catalyzed diene-aldehyde cyclocondensation (LACDAC) and asym. allylation methodol. are also noteworthy.

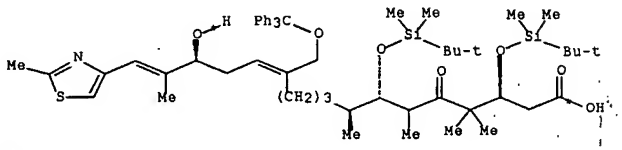
RX(3) OF 59 *H* ===> *I*...



H

(3) →

RX(1) OF 1 **A** ===> **B**



A

(1)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(1) RCT A ***201136-77-8***

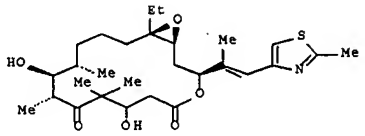
STAGE(1)
RGT C 121-44-8 Et3N, D 4136-95-2 2,4,6-Cl3C6H2COCl
SOL 109-99-9 THF

STAGE(2)
RGT E 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

PRO B ***209260-71-9***

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

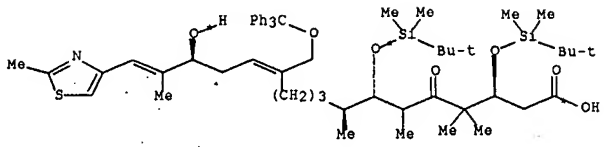
L90 ANSWER 26 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 128:101936 CASREACT Full-text
TITLE: Total synthesis of 26-hydroxyepothilone B and related analogs
AUTHOR(S): Nicolaou, K. C.; Ninkovic, Sacha; Finlay, M. Ray V.; Sarabia, Francisco; Li, Tianhu
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, California, 92093, USA
SOURCE: Chemical Communications (Cambridge) (1997), (24), 2343-2344
CODEN: CHCOFS; ISSN: 1359-7345
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB A series of 26-substituted epothilones B, e.g. I, were constructed by total synthesis involving a selective Wittig olefination, an aldol reaction and a macrolactonization as key steps.

RX(2) OF 2 **G** ===> **H**



G

(2)

methodology for the rapid, highly selective and convergent construction of epothilone Bepothilone B and analogs

AUTHOR(S): Nicolaou, K. C.; Hepworth, David; Finlay, M. Ray V.; Paul King, N.; Werschkun, Barbara; Bigot, Antony

CORPORATE SOURCE: Department of Chemistry, The Skaggs Inst. Chem. Biol., The Scripps Res. Inst., La Jolla, CA, 92037, USA

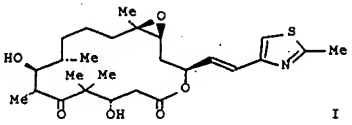
SOURCE: Chemical Communications (Cambridge) (1999), (6), 519-520
CODEN: CHCOFS; ISSN: 1359-7345

PUBLISHER: Royal Society of Chemistry

DOCUMENT TYPE: Journal

LANGUAGE: English

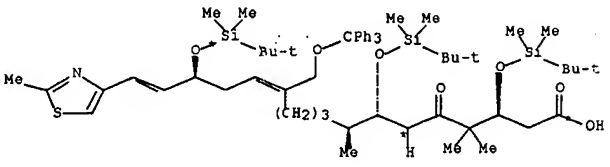
GI



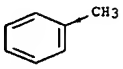
I

AB During a synthesis of 16-desmethylepothilone B (I) new methods for the convergent and highly stereoselective synthesis of epothilone B and analogs were developed.

RX(18) OF 37 ***BK*** + BL ===> ***BQ***



BK



BL

(18) →

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(18) RCT BK ***226940-48-3***, BL 108-88-3

STAGE(1)
RGT BR 4136-95-2 2,4,6-Cl3C6H2COCl, BC 121-44-8 Et3N
SOL 109-99-9 THF

STAGE(2)
CAT 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

PRO BQ ***226940-49-4***
NTE key step

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 25 OF 28 CASREACT COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 129:189151 CASREACT Full-text

TITLE: Total synthesis of 26-hydroxy-epothilone B and related analogs via a macrolactonization based strategy

AUTHOR(S): Nicolaou, K. C.; Finlay, M. Ray V.; Ninkovic, Sacha; Sarabia, Francisco

CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA

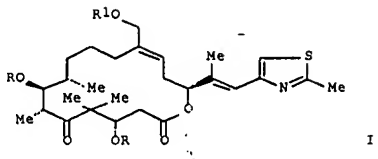
SOURCE: Tetrahedron (1998), 54(25), 7127-7166
CODEN: TETRAB; ISSN: 0040-4020

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



I

AB The chemical synthesis of a series of 26-substituted epothilones B was described. Fully protected 26-hydroxydesoxy-epothilone B I (R = SiMe2CMe3, R1 = CPh3), prepared via a macrolactonization strategy, served as a common precursor to the designed epothilones described. The synthesized compds. were members of a large epothilone library of a number of antitumor agents.

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(4) RCT T ***241129-39-5***

STAGE(1)
RGT V 84033-23-8 Benzoyl chloride, trichloro-, W 121-44-8 Et3N
SOL 109-99-9 THF

STAGE(2)
RGT X 1122-58-3 4-DMAP
SOL 108-88-3 PhMe, 109-99-9 THF

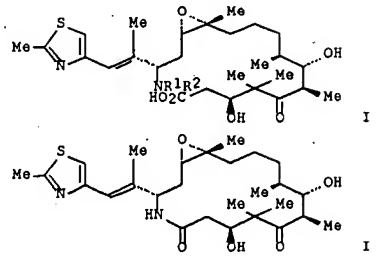
PRO U ***241129-40-8***

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 23 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 131:31829 CASREACT Full-text
TITLE: A process for the preparation of ring-opened epothilone intermediates which are useful for the preparation of epothilone analogs
INVENTOR(S): Kim, Soong-Hoon; Borzilleri, Robert M.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9927890	A2	19990610	WO 1998-US25408	19981130
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6365749	B1	20020402	US 1998-170582	19981013
CA 2312098	A1	19990610	CA 1998-2312098	19981130
EP 1035824	A1	20000920	EP 1998-960564	19981130
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
AU 739380	B2	20011011	AU 1999-16134	19981130
JP 2003522722	T	20030729	JP 2000-522878	19981130
ZA 9810993	A	20000601	ZA 1998-10993	19981201
PRIORITY APPLN. INFO.:			US 1997-67550P	19971204
			WO 1998-US25408	19981130

OTHER SOURCE(S): MARPAT 131:31829
GI

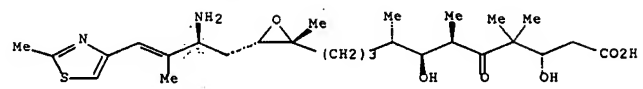


I

I

AB A process to produce ring opened epothilones (I) [NR1R2 = N3, (un)substituted amine] and their use in the preparation of epothilone analogs (II) is presented. Thus, epothilone B is cleaved with NaN3, azide reduced to amine and macrolactamized with diphenylphosphoryl azide to give II in 40% yield.

RX(3) OF 6 ...*F* ===> *J*



F

(3) →

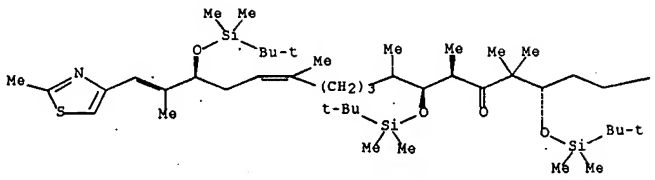
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(3) RCT F ***219990-25-7***
RGT K 26386-88-9 (PhO)2P(O)N3
PRO J ***219989-84-1***
SOL 68-12-2 DMF

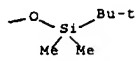
L90 ANSWER 24 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 131:31819 CASREACT Full-text
TITLE: Synthesis of 16-desmethylepothilone B: improved

RX(2) OF 215 ...D ===> B

PAGE 1-A



PAGE 1-B



D

(2)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(2) RCT D 193146-51-9
PRO B 152044-54-7
NTE lit. ref.

REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

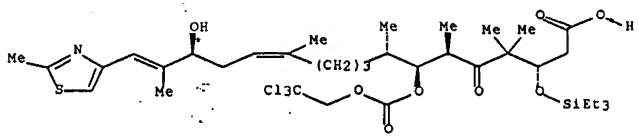
L90 ANSWER 22 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 131:286299 CASREACT Full-text
TITLE: New Chemical Synthesis of the Promising Cancer Chemotherapeutic Agent 12,13-Desoxyepothilone B: Discovery of a Surprising Long-Range Effect on the Diastereoselectivity of an Aldol Condensation
AUTHOR(S): Harris, Christina R.; Kuduk, Scott D.; Balog, Aaron; Savin, Ken; Glunz, Peter W.; Danishefsky, Samuel J.
CORPORATE SOURCE: Laboratory for Bioorganic Chemistry, The Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA

SOURCE: Journal of the American Chemical Society (1999), 121(30), 7050-7062
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

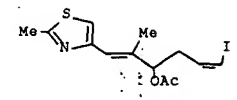
AB The epothilones are naturally occurring cytotoxic mols. that possess the remarkable ability to arrest cell division through the stabilization of microtubule assemblies. In vivo studies with 12,13-desoxyepothilone B (dEpoB) (I), have established that the desoxy compound is well tolerated and virtually curative against a variety of sensitive and resistant xenograft tumors in animal models. In light of these discoveries, a chemical synthesis of dEpoB would be able to support a serious and substantial discovery research program directed toward the clin. development of this mol. The overall strategy for this endeavor assumed the ability to synthesize dEpoB from three constructs which include an achiral β,δ-diketo ester construct A (II), an (S)-2-methylpentenal moiety B (III), and the thiazoyl-containing vinyl iodide moiety C (IV). It was envisioned that a diastereoselective aldol condensation between an achiral C5-C6 (Z)-metalloenolate derived from construct A and an (S)-2-methylalkanal fragment, B, would generate the desired C6-C7 bond. Second, a B-alkyl Suzuki coupling between the vinyl iodide construct C and an alkyl borane would form the C11-C12 bond. Finally, a late-stage reduction of the C3 ketone to the requisite C3 alc. with high asym. induction would permit introduction of the β,δ-diketo ester fragment A, into the synthesis as a readily accessible achiral building block. The governing concepts the new synthesis are described.

RX(4) OF 5 T ===> U

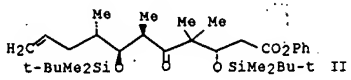


T

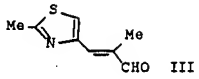
(4)



I



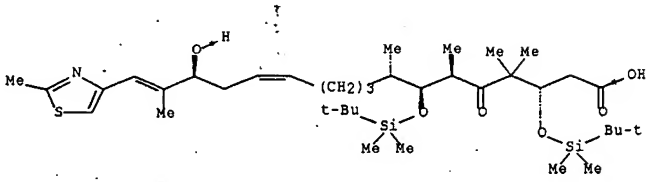
II



III

AB The enantioselective total synthesis of epothilone A was achieved via the catalytic coupling of I and II. The key step in the preparation of I was the catalytic cyanosilylation of III. II was prepared via a catalytic organic acetalization followed by an aldol reaction.

RX(5) OF 6 ...C ===> AC



C

(5)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(5) RCT C ***188730-19-0***

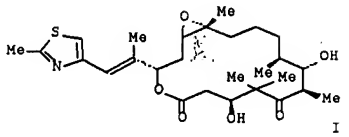
STAGE(1)
RGT AD 4136-95-2 2,4,6-Cl3C6H2COCl, AE 121-44-8 Et3N

SOL 109-99-9 THF

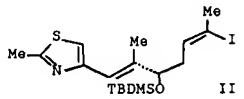
STAGE(2)
RGT AF 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

PRO AC ***186692-84-2***
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 21 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 131:351125 CASREACT Full-text
TITLE: Syntheses of (-)-epothilone B
AUTHOR(S): Schinzer, Dieter; Bauer, Armin; Schieber, Jennifer
CORPORATE SOURCE: Chemisches Institut der Otto-von-Guericke-Universitat, Magdeburg, D-39106, Germany
SOURCE: Chemistry--A European Journal (1999), 5(9), 2492-2500
CODEN: CEUJED; ISSN: 0947-6539
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I



II

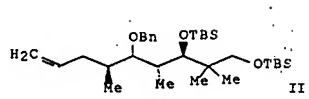
AB Two efficient routes for the total synthesis of (-)-epothilone B (I) are reported. One strategy is based on ring-closing metathesis, and a second synthesis on a macrolactonization. The key fragments are available on large scale to provide sufficient material for biol. tests. Thiazole fragment II (TBDMS = SiMe2CMe3) was obtained by an improved route starting from (S)-malic acid. The first synthesis is based on our preceding paper. The critical trisubstituted double bond C12-13 in our second approach was constructed by a highly efficient Pd-mediated coupling reaction. Ring closure was achieved by macrolactonization.

STAGE(2)

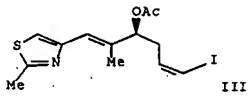
STAGE(3)
SOL 141-78-6 AcOEt

PRO AL ***219989-84-1***
NTE PHOSPHATE BUFFER USED INSECOND STAGE
REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 19 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 133:266631 CASREACT Full-text
TITLE: Total Synthesis of Epothilone A
AUTHOR(S): Zhu, Bin; Panek, James S.
CORPORATE SOURCE: Department of Chemistry and the Center for Streamlined Synthesis Metcalf Center for Science and Engineering, Boston University, Boston, MA, 02215, USA
SOURCE: Organic Letters (2000), 2(17), 2575-2578
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



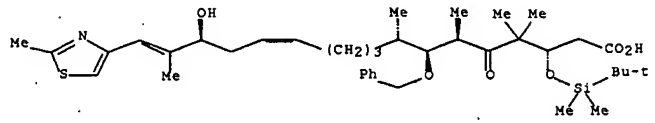
II



III

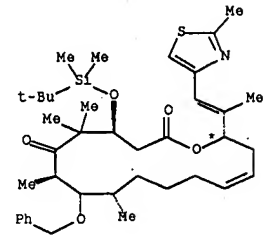
AB Epothilones A (I) and B are potent antitumor natural products with a Taxol-like mechanism of action. A total synthesis of I is reported, which utilized chiral silane-based bond construction methodol. to introduce the key C-6 and C-7 stereocenters of fragment (II). The C-15 stereocenter of fragment (III) was established by a lipase-mediated kinetic resolution The fragments were assembled with a Suzuki coupling reaction and an aldol condensation and cyclized with a Yamaguchi-type macrolactonization reaction.

RX(4) OF 6 ***V*** ===> ***W***



V

(4)



W
YIELD 73%

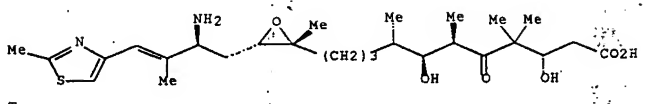
RX(4) RCT V ***297131-85-2***

STAGE(1)
RGT X 4136-95-2 2,4,6-Cl3C6H2COCl, Y 121-44-8 Et3N
SOL 109-99-9 THF

STAGE(2)
RGT Z 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

PRO W ***297131-86-3***
NTE stereoselective
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 20 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 132:251011 CASREACT Full-text
TITLE: Enantioselective total synthesis of epothilone A using multifunctional asymmetric catalyses
AUTHOR(S): Sawada, Daisuke; Shibasaki, Masakatsu
CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, 113-0033, Japan
SOURCE: Angewandte Chemie, International Edition (2000), 39(1), 209-213
CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



T

(8)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(8) RCT T ***219990-25-7***

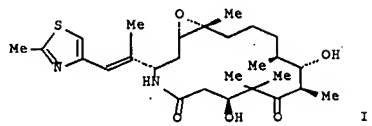
STAGE(1)
SOL 68-12-2 DMF

STAGE(2)
RGT D 144-55-8 NaHCO3, Z 26386-88-9 (PhO)2P(O)N3

PRO I ***219989-84-1***

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

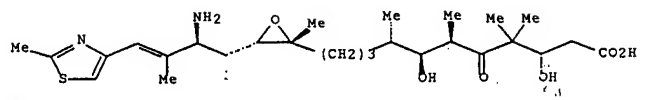
L90 ANSWER 18 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 133:321737 CASREACT Full-text
TITLE: A Novel Application of a Pd(0)-Catalyzed Nucleophilic Substitution Reaction to the Regio- and Stereoselective Synthesis of Lactam Analogues of the Epothilone Natural Products
AUTHOR(S): Borzilleri, Robert M.; Zheng, Xiaoping; Schmidt, Robert J.; Johnson, James A.; Kim, Soong-Hoon; DiMarco, John D.; Fairchild, Craig R.; Gougoutas, Jack Z.; Lee, Francis Y. F.; Long, Byron H.; Vite, Gregory D.
CORPORATE SOURCE: Divisions of Discovery Chemistry Oncology Drug Discovery and Analytical Research and Development, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA
SOURCE: Journal of the American Chemical Society (2000), 122(37), 8890-8897
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Several lactam analogs of the epothilones were prepared using a concise semisynthetic approach starting with the unprotected natural products. Highlighted in this strategy is a novel regio- and stereoselective Pd(0)-catalyzed azidation reaction of a macrocyclic lactone. Subsequent reduction and macrolactamization of the resulting azide acid intermediates provided the desired macrolactams in satisfactory overall yields. The entire three-step sequence was streamlined into a "one-pot" process for the epothilone B-lactam, BMS-247550 (I), which is currently undergoing phase I clin. trials. An initial total synthesis route to prepare the lactam analog of epothilone C was completed and compared to the more direct semisynthesis approach. All of the lactam analogs were evaluated in vitro and the results are discussed.

RX(10) OF 115 ...***AJ*** ===> ***AL***...



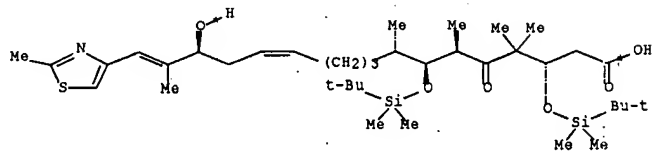
AJ

(10)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(10) RCT AJ ***219990-25-7***

STAGE(1)
RGT AM 26386-88-9 (PhO)2P(O)N3, AB 144-55-8 NaHCO3
SOL 68-12-2 DMF



CG

(27)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(27) RCT CG ***188730-19-0***

STAGE(1)
RGT CS 4136-95-2 2,4,6-Cl3C6H2COCl, BE 121-44-8 Et3N
SOL 109-99-9 THF

STAGE(2)
RGT BF 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

PRO CR ***186692-84-2***
NTE STEREOSELECTIVE
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 17 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 133:362657 CASREACT Full-text
TITLE: A process for the reduction of oxiranyl epothilones to olefinic epothilones
INVENTOR(S): Kim, Soong-Hoon; Johnson, James A.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Co., USA
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000071521	A1	20001130	WO 2000-US13253	20000515

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI,

SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6320045	B1	20011120	US 1999-316796	19990521
CA 2375029	A1	20001130	CA 2000-2375029	20000515
EP 1178968	A1	20020213	EP 2000-930725	20000515
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003500394	T	20030107	JP 2000-619778	20000515
IN 2001MN01106	A	20070420	IN 2001-MN1106	20010912
MX 2001PA11053	A	20020722	MX 2001-PA11053	20011030
PRIORITY APPLN. INFO.:			US 1999-316796	19990521
			US 1997-67549P	19971204
			US 1998-82563P	19980421
			US 1998-170581	19981013
			WO 2000-US13253	20000515

OTHER SOURCE(S): MARPAT 133:362657
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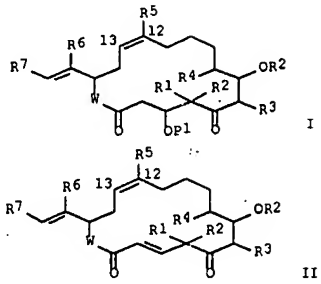


I

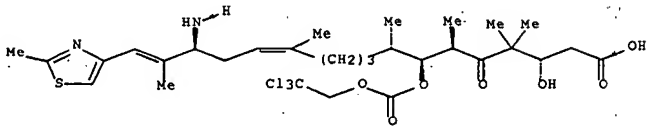
II

AB 12(13)-Olefinic epothilones, such as I and II [R1-6 = H, alkyl, aryl; R1R2 = cycloalkyl; R7 = H, alkyl, aryl, cycloalkyl, heterocyclyl; P1, P2 = H, alkyl, alkanoyl, aroyl, silyl, etc.; W = O, NR8; R8 = H, OH, alkyl], were prepared via reduction of the corresponding 12,13-epoxyepothilones using a metal or metal-assisted reagent. The metal or metal-assisted reagent was selected from the group consisting of reactive metallocenes, [N2C(CO2Me)2, cat Rh2(OAc)4], [N2C(CO2Me)2, cat[(n-C7H15CO2)2Rh]2], [Zn-Cu, EtOH]', [Mg(Hg), MgBr], Cr, [FeCl3, n-BuLi], [TiCl3, LiAlH4], [TiCl4, Zn], [WCl6, LiAlH4], [NbCl5, NaAlH4], [VCl3,Zn], or [WCl6, n-BuLi]. Thus, epothilone A, a 12,13-epoxyepothilone, was reduced using magnesium turnings and titanocene dichloride in THF to give epothilone C, a 12(13)-(Z)-olefin, in 80% yield.

RX(8) OF 18 ...T ===> I...

efficient and was amenable to the production of significant quantities of these lactams. Using our fully synthetically derived lactams, in vitro and in vivo studies were conducted in comparison with advanced clin. candidates, 12,13-desoxyepothilone B and 12,13-desoxyepothilone F, also derived by total synthesis.

RX(2) OF 2 2 *J* ===> *K* + *L*



2 J

(2)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(2) RCT J ***350042-12-5***

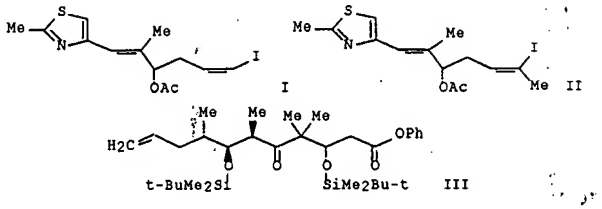
STAGE(1)
RGT M 7087-68-5 EtN(Pr-i)2, N 148893-10-1 1H-1,2,3-Triazolo[4,5-b]pyridinium, 1-[bis(dimethylamino)methylene]-, hexafluorophosphate(1-), 3-oxide, O 39968-33-7 3H-1,2,3-Triazolo[4,5-b]pyridine, 3-hydroxy-
SOL 68-12-2 DMF, 75-09-2 CH2Cl2

STAGE(2)
RGT P 64-19-7 AcOH
SOL 7732-18-5 Water, 109-99-9 THF

PRO K ***277749-43-6***, L ***350042-20-5***
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 16 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 134:56502 CASREACT Full-text
TITLE: Enantioselective Total Synthesis of Epothilones A and B Using Multifunctional Asymmetric Catalysis
AUTHOR(S): Sawada, Daisuke; Kanai, Motomu; Shibasaki, Masakatsu
CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, The

University of Tokyo, Bunkyo-ku Tokyo, 113-0033, Japan
SOURCE: Journal of the American Chemical Society (2000), 122(43), 10521-10532
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB An enantioselective total synthesis of epothilones A and B using multifunctional asym. catalysis such as a cyanosilylation of an aldehyde, an aldol reaction of an unmodified ketone with an aldehyde, and a protonation in the conjugate addition of a thiol to an α,β-unsatd. thioester has been achieved. Epothilones A and B were divided into fragment A (I), fragment B (II), and fragment C (III). A catalytic asym. synthesis of fragments A and B was accomplished using a catalytic asym. cyanosilylation as a key step. An enantiocontrolled synthesis of fragment C was achieved in two ways. One is the use of a direct catalytic asym. aldol reaction of an unmodified ketone with an aldehyde as a key step, and the other utilizes a catalytic asym. protonation in the conjugate addition of a thiol to an α,β-unsatd. thioester as a key step. Suzuki cross-coupling of fragment A with fragment C followed by Yamaguchi lactonization as key steps led to an enantiocontrolled synthesis of epothilone A. On the other hand, Suzuki cross-coupling of fragment B with fragment C followed by Yamaguchi lactonization accomplished an enantiocontrolled synthesis of epothilone B.

RX(27) OF 319 ...*CG* ===> *CR*

TITLE: Methodology based on chiral silanes in the synthesis of polypropionate-derived natural products - total synthesis of epothilone A

AUTHOR(S): Zhu, Bin; Panek, James S.

CORPORATE SOURCE: R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ, 08869, USA

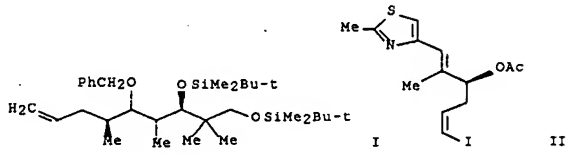
SOURCE: European Journal of Organic Chemistry (2001), (9), 1701-1714
CODEN: EJOCFK; ISSN: 1434-193X

PUBLISHER: Wiley-VCH Verlag GmbH

DOCUMENT TYPE: Journal

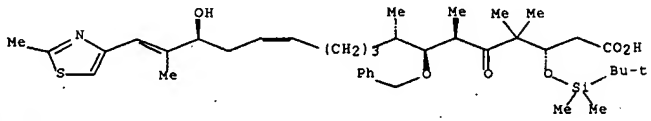
LANGUAGE: English

GI



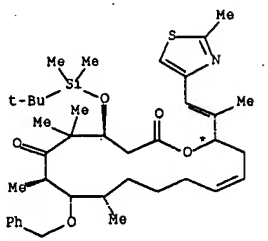
AB Epothilones A and B are natural products with potent antitumor activity. These compds. have a Taxol-like mechanism of action against tumor cells. A total synthesis of epothilone A is reported, which is based on the synthesis and union of two advanced fragments: C3-C11 fragment I and C12-C21 fragment II. Bond construction methodol. based on chiral silanes was utilized to introduce the key C6 and C7 stereocenters of fragment I. A lipase-mediated kinetic resolution established the C15 stereocenter of fragment II. The 16-membered lactone was constructed using a three-step sequence: an intermol. B-alkyl Suzuki coupling of I and II, an aldol condensation, and a Yamaguchi-type macrolactonization reaction.

RX(6) OF 7 ***AD*** ===> ***AE***



AD

(6)



AE
YIELD 73%

RX(6) RCT AD ***297131-85-2***
RGT AF 121-44-8 Et3N, AG 4136-95-2 2,4,6-Cl3C6H2COCl
PRO AE ***297131-86-3***
SOL 109-99-9 THF

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 15 OF 28 CASREACT COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 135:107175 CASREACT Full-text

TITLE: On the Interactivity of Complex Synthesis and Tumor Pharmacology in the Drug Discovery Process: Total Synthesis and Comparative in Vivo Evaluations of the 15-Aza Epothilones

AUTHOR(S): Stachel, Shawn J.; Lee, Chul Bom; Spassova, Maria; Chappell, Mark D.; Bornmann, William G.; Danishefsky, Samuel J.; Chou, Ting-Chao; Guan, Yongbiao

CORPORATE SOURCE: Laboratories for Bioorganic Chemistry Preclinical Pharmacology and the Preparative Synthesis Core Facility, The Sloan-Kettering Institute for Cancer, Research, New York, NY, 10021, USA

SOURCE: Journal of Organic Chemistry (2001), 66(12), 4369-4378
CODEN: JOCEAH; ISSN: 0022-3263

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The total syntheses of 12,13,15-desoxy-15(S)-aza-epothilone B (aza-dEpoB; dEpoB-lactam) and 12,13,15-desoxy-15(R)-aza-epothilone B (15-epi-aza-dEpoB; 15-epi-dEpoB-lactam) have been accomplished via a highly convergent strategy. We have also successfully oxidized 12,13,15-desoxy-15(S)-aza-epothilone B to aza-epothilone B (aza-EpoB; EpoB-lactam). Aza-epothilone B has been advanced to phase I clin. trials by the Bristol-Myers Squibb group. Our synthesis is

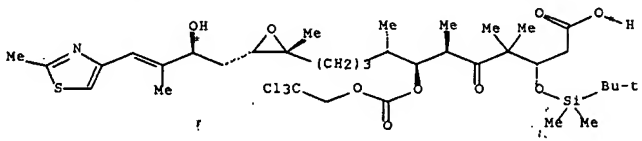
PRO K ***219989-84-1***
NTE alternative prepn. gave lower yields
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 13 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 135:180640 CASREACT Full-text
TITLE: The 12,13-diol cyclization approach for a truly stereocontrolled total synthesis of epothilone B and the synthesis of a conformationally restrained analog
AUTHOR(S): Martin, Harry J.; Pojarliev, Peter; Kahlig, Hanspeter; Mulzer, Johann
CORPORATE SOURCE: Institut fur Organische Chemie der Universitat Wien, Vienna, 1090, Austria
SOURCE: Chemistry--A European Journal (2001), 7(10), 2261-2271
CODEN: CEUJED; ISSN: 0947-6539
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A highly convergent and stereocontrolled synthesis of epothilone B (I) has been developed. The epoxide moiety in I was generated by regioselective mesylation and base treatment of the 12,13-diol II which was formed by a chelate Cram controlled Grignard addition of (3S)-Br(CH2)3CHMeCH:CH2 and Me ketone III. Both fragments were synthesized from the chiral carbon pool precursors (S)-citronellol and (S)-lactic acid, resp. A highly diastereoselective aldol addition of epoxy-aldehyde IV and the known Southern hemisphere ketone (S)-MeCH2COCMe2CH(OSiMe2CMe3)CH2CH:CH2 delivered the full carbon skeleton, containing all the stereogenic centers of I. Functional group manipulation, macrolactonization and removal of two protecting groups then yielded I. The spatial closeness of the C4-β-Me and C6-Me group in the crystal structure of I inspired the authors to connect them through a methylene bridge to give a cyclohexanone derivative Thus, the Northern hemisphere aldehyde IV was added to the enolate of a cyclohexanone derivative Further manipulations and macrolactonization delivered the conformationally restrained epothilone derivative V.

RX(2) OF 2 ***G*** ===> ***H***



G

(2) →

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

PAGE 1-B

—Bu-t

PAGE 2-A

H
YIELD 65%

RX(2) RCT G ***263761-19-9***
RGT I 121-44-8 Et3N, J 4136-95-2 2,4,6-Cl3C6H2COCl, K 1122-58-3 4-DMAP
PRO H ***263761-23-5***
SOL 108-88-3 PhMe
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 14 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 135:137326 CASREACT Full-text

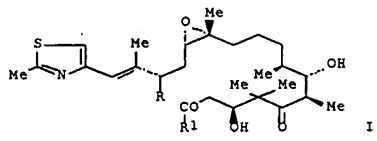
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(8) RCT X ***219990-25-7***
RGT AC 26386-88-9 (PhO)2P(O)N3, J 144-55-8 NaHCO3
PRO AB ***219989-84-1***
SOL 68-12-2 DMF
REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 12 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 135:257087 CASREACT Full-text
TITLE: A process for the preparation of epothilone analogs and intermediates
INVENTOR(S): Li, Wen Sen; Thornton, John E.; Guo, Zhenrong; Swaminathan, Shankar; McConlogue, Gary W.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070716	A1	20010927	WO 2001-US7749	20010312
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2404212	A1	20010927	CA 2001-2404212	20010312
EP 1265878	A1	20021218	EP 2001-918544	20010312
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
HU 200300693	A2	20030828	HU 2003-693	20010312
JP 2003528090	T	20030924	JP 2001-568920	20010312
IN 2002MN01074	A	20050304	IN 2002-MN1074	20020808
MX 2002PA09165	A	20040812	MX 2002-PA9165	20020919
PRIORITY APPLN. INFO.:			US 2000-528526	20000320
			WO 2001-US7749	20010312

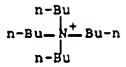
OTHER SOURCE(S): MARPAT 135:257087
GI



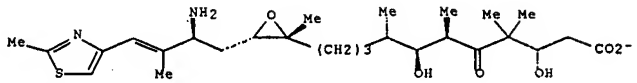
I

AB The present invention relates to a process for the preparation of epothilone analogs, such as I (RR1 = NH), by initially forming novel ring-opened epothilones and carrying out a macrolactamization reaction thereon. The subject process is amenable to being carried out in a single reaction vessel without isolation of the intermediate compound and provides at least about a three-fold increase in yield over prior processes for preparing the desired epothilone analogs. Thus, ring opening of epothilone B was achieved using NaN3, PMe3 and Bu4N+Cl- in THF in the presence of Pd2(dba)3.CHCl3 to form TBA salt I (R = NH2, R1 = O-.Bu4N+) in 93% yield. The ring opened epothilone B TBA salt the underwent intramol. macrolactamization using K2CO3, HOBt, and EDCI in THF and DMF to form lactam I (RR1 = NH) in 92.7% % yield.

RX(2) OF 4 ...***C*** ===> ***K***



C: CM 1



C: CM 2

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(2) RCT C ***361204-09-3***

STAGE(1)
RGT L 1310-58-3 KOH
SOL 109-99-9 THF, 68-12-2 DMF

STAGE(2)
RGT M 2592-95-2 1-Benzotriazolol, N 25952-53-8 EDAP

SOL 109-99-9 THF

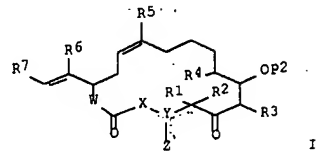
STAGE(2)
RGT AW 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

PRO AU ***241129-40-8***

L90 ANSWER 11 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 135:371566 CASREACT Full-text
TITLE: Process for reduction of oxiranyl epothilones to olefinic epothilones
INVENTOR(S): Kim, Soong-hoon; Johnson, James A.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Co., USA
SOURCE: U.S., 10 pp., Cont.-in-part of U.S. Ser. No. 170,581.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6320045	B1	20011120	US 1999-316796	19990521
CA 2375029	A1	20001130	CA 2000-2375029	20000515
WO 2000071521	A1	20001130	WO 2000-US13253	20000515
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1178968	A1	20020213	EP 2000-930725	20000515
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
HU 2002001467	A2	20021028	HU 2002-1467	20000515
JP 2003500394	T	20030107	JP 2000-619778	20000515
IN 2001MN01106	A	20070420	IN 2001-MN1106	20010912
MX 2001PA11053	A	20020722	MX 2001-PA11053	20011030
PRIORITY APPLN. INFO.:			US 1997-67549P	19971204
			US 1998-82563P	19980421
			US 1998-170581	19981013
			US 1999-316796	19990521
			WO 2000-US13253	20000515

OTHER SOURCE(S): MARPAT 135:371566
GI



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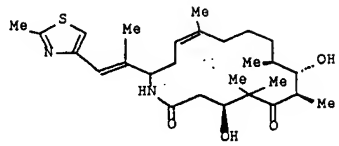
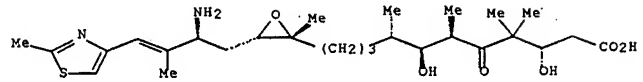


II

AB This process produced epothilones I (W = O, NR8; R1-R6 = H, (un)substituted alkyl or aryl and R1 and R2 can be cycloalkyl; R7 = H, (un)substituted alkyl, aryl, cycloalkyl or 4-7 membered heterocyclic N-, O-, or S-containing rings; R8 = H, (un)unsubstituted alkyl, OH, (un)unsubstituted O-alkyl; X = CH2 or XY = CH=CH; Z = H or OP1 where P1, P2 = H, (un)substituted alkyl, alkanoyl, aroyl, trialkyl(aryl)silyl) from oxiranyl epothilones via the reaction of the oxiranyl moiety with a metal or metal-assisted reagent selected from the group consisting of reactive metallocenes, or (WCl6, n-BuLi). Thus II was prepared in 29% yield in a multistep reaction from epothilone B via the aminoheptadecenoic acid that cyclized to the oxiranyl azaepothilone intermediate which was reacted with WCl6 in THF and n-BuLi in hexane.

RX(8) OF 16 ...***X*** ===> ***AB***...



X

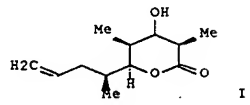
(8)

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002012534	A2	20020214	WO 2001-US25112	20010809
WO 2002012534	A3	20020906		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2001092991	A2	20011206	WO 2001-US17352	20010529
WO 2001092991	A3	20020808		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001075012	A5	20011211	AU 2001-75012	20010529
CA 2417358	A1	20020214	CA 2001-2417358	20010809
AU 2001083275	A5	20020218	AU 2001-83275	20010809
EP 1307579	A2	20030507	EP 2001-962062	20010809
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004520008	T	20040708	JP 2002-517818	20010809

PRIORITY APPLN. INFO.:
US 2000-224038P 20000809
US 2000-237382P 20001004
US 2000-248387P 20001113
US 2001-867845 20010529
US 2000-207331P 20000530
WO 2001-US17352 20010529
WO 2001-US25112 20010809

OTHER SOURCE(S): MARPAT 136:183657

GI

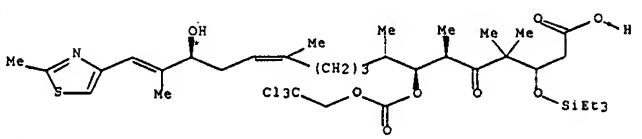


I

AB The present invention relates to compds., such as I, made by a subset of modules from one or more polyketide synthase ("PKS") genes that are used as starting material in the chemical synthesis of novel mols., particularly naturally occurring polyketides or derivs. thereof. The biol. derived intermediates ("bio-intermediates") generally represent particularly difficult compds. to synthesize using traditional chemical approaches due to one or more

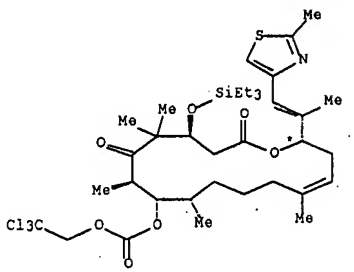
stereocenters. In one aspect of the invention, an intermediate in the synthesis of epothilone is provided that feeds into the synthetic protocol of Danishefsky and co-workers. In another aspect of the invention, intermediates in the synthesis of discodermolide are provided that feed into the synthetic protocol of Smith and co-workers. By taking advantage of the inherent stereochem. specificity of biol. processes, the syntheses of key intermediates and thus the overall syntheses of compds. like epothilone and discodermolide are greatly simplified.

RX(12) OF 142 ...AQ ===> AU...



AQ

(12)



AU

RX(12) RCT AQ 241129-39-5

STAGE(1)
RGT AV 4136-95-2 2,4,6-Cl3C6H2COCl, E 121-44-8 Et3N

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10041470	A1	20020228	DE 2000-10041470	20000818

PRIORITY APPLN. INFO.: DE 2000-10041470 20000818
OTHER SOURCE(S): MARPAT 136:216592
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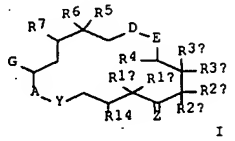

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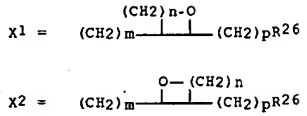
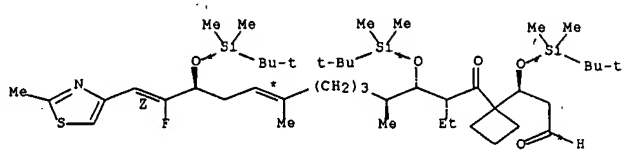
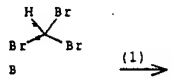


AB The present invention describes new 6-alkenyl- and 6-alkynylepothilone derivs., e.g., I [R1a, R1b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R1aR1b = (CH2)r, CH2OCH2; r = 1 - 5; R2a = H, C1-10-alkyl, aryl, C7-20-aralkyl, (CH2)m-C.tplbond.C-(CH2)pR26, (CH2)m-C:C-(CH2)pR26, X1, X2; n = 0 - 5; p = 0 - 3; m = 0 - 4; R2b = (CH2)m-C.tplbond.C-(CH2)pR26, (CH2)m-C:C- (CH2)pR26, X1, X2; R3a = H, C1-10-alkyl, aryl, C7-20-aralkyl; R3b = O-protecting group; R4 = H, C1-10-alkyl, aryl, C7-20-aralkyl, halogen, OH, O-protecting group, CN; R5 = H, C1-10-alkyl, aryl, C7-20-aralkyl, (CH2)s-T; S = 1 - 4; T = OH, O-protecting group, halogen; R6R7 = C(R33)2, NR32 AY = OC(:O), OCH2, CH2C(:O), NR29C(:O), NR29SO2; DE = CH2CH2, CH2O, OCH2; G = X:CR8-, bicyclic or tricyclic aryl; X = O, (O-alkyl)2, etc.; Z = H, H,OH, H,O-protective group; R8 = H, halogen, CN, C1-20-alkyl, aryl, C7-20-aralkyl; R14 = H, OH, halogen, O-SO2-alkyl, O-SO2-aryl, O-SO2-aralkyl; R26 = H, C1-10-alkyl, aryl, C7-20-aralkyl, C1-10-acyl, OH, O-protecting group; R29 = H, C1-20-alkyl; R32 = H, C1-4-alkyl, C1-4-acyl; R33 = H, halogen], which interact with tubulins by stabilizing the formed microtubulins (no data). I are able specifically to affect cell division and are suitable, for example for the treatment of malignant tumors ovarial -, stomach -, colon -, adeno -, chest -, lungs -, head and neck carcinoma, malignant melanoma, acute lymphocytic and myelocytic leukemia. In addition I are suitable for the anti-angiogenesis therapy as well as for the treatment of chronic ignitable illnesses (psoriasis, arthritis). For the avoidance of uncontrolled cell rampant growths on as well as the better compatibility of medical implants I can be up and/or brought into polymers materials. According to invention, I can be used alone or for the achievement of additive or synergistic effects in combination with further principles and substance classes applicable in the tumor therapy. Exptl. data from patents PCT/EP00/01333 and PCT/IB00/00657 are reproduced here.

RX(1) OF 1 **A** + B ===> **C**



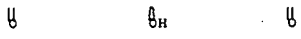
A



B

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

PAGE 2-A



C

RX(1) RCT A ***289501-50-4***, B 75-25-2
RGT D 1310-73-2 NaOH
PRO C ***402476-95-3***
CAT 56-37-1 PhCH2NEt3 Cl
SOL 7732-18-5 Water, 64-17-5 EtOH

L90 ANSWER 10 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 136:183657 CASREACT Full-text
TITLE: Process for the biomediated preparation of intermediates for use in the synthesis of polyketides, such as epothilone D and discodermolide
INVENTOR(S): Santi, Daniel V.; Ashley, Gary; Myles, David C.
PATENT ASSIGNEE(S): Kosan Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 129 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(2) RCT C ***361204-09-3***

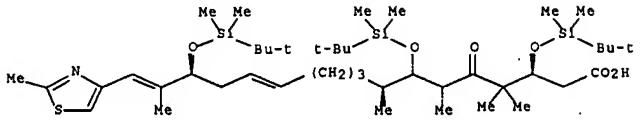
STAGE(1)
RGT K 584-08-7 K2CO3
SOL 109-99-9 THF, 68-12-2 DMF

STAGE(2)
RGT L 2592-95-2 1-Benzotriazolol, M 25952-53-8 EDAP

PRO J ***219989-84-1***
NTE alternative prepns. gave lower yields

L90 ANSWER 8 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 136:318824 CASREACT Full-text
TITLE: Synthetic and semisynthetic analogs of epothilones: chemistry and biological activity
AUTHOR(S): Altmann, Karl-Heinz; Blommers, Marcel J. J.; Caravatti, Giorgio; Florsheimer, Andreas; Nicolaou, Kyriacos C.; O'Reilly, Terrence; Schmidt, Alfred; Schinzer, Dieter; Wartmann, Markus
CORPORATE SOURCE: TA Oncology Research, Novartis Pharma AG, Basel, CH-4002, Switz.
SOURCE: ACS Symposium Series (2001), 796(Anticancer Agents), 112-130
CODEN: ACSMC8; ISSN: 0097-6156
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Epothilones A and B are naturally occurring microtubule depolymn. inhibitors, which exhibit potent in vitro antiproliferative activity. Epothilone B is a 3-30-fold more potent inhibitor of human cancer cell growth than paclitaxel in paclitaxel-sensitive cancer cell lines and in paclitaxel-resistant lines exceeds paclitaxel activity by 102 - 103-fold. In addition, epothilone B exhibits potent in vivo antitumor activity even in multidrug-resistant tumor models. In order to gain a better understanding of the structural requirements for epothilone-mediated cytotoxicity and antitumor activity and to discover analogs with similar potency but perhaps better tolerability in vivo, we have investigated a series of structural modifications involving the epoxide site (C12/C13) and the heterocyclic side-chain of epothilones. In this paper we present the synthesis of these analogs and we discuss the impact of such modifications on tubulin polymerization activity as well as cytotoxicity in vitro.

RX(32) OF 320 ...CP ==> CR...



CP

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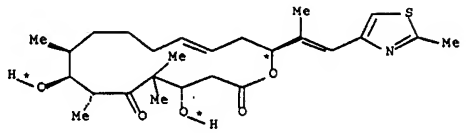


CR

RX(32) RCT CP ***335160-11-7***

STAGE(1)
RGT CS 429-41-4 Bu4N.F
SOL 109-99-9 THF

STAGE(2)
RGT CT 4136-95-2 2,4,6-Cl3C6H2COCl, AP-121-44-8 Et3N, CA 1122-58-3 4-DMAP
SOL 109-99-9 THF, 108-88-3 PhMe

STAGE(3)
RGT R 76-05-1 F3CCO2H
SOL 75-09-2 CH2Cl2

PRO CR ***188260-10-8***
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 9 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 136:216592 CASREACT Full-text
TITLE: Procedures for the production of 12,13-cyclopropylepothilone derivatives, as well as for their use in pharmaceutical preparations
PATENT ASSIGNEE(S): Schering Ag, Germany
SOURCE: Ger. Offen., 64 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

PAGE 2-A

I
YIELD 33%

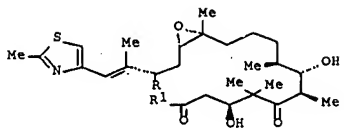
RX(30) RCT DH ***472962-13-3***
RGT AN 4136-95-2 2,4,6-Cl3C6H2COCl, AO 121-44-8 Et3N, AP 1122-58-3 4-DMAP
PRO I ***472962-14-4***
SOL 109-99-9 THF, 108-88-3 PhMe
NTE stereoselective, Yamaguchi macrocyclization
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 7 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 137:140388 CASREACT Full-text
TITLE: A process for the preparation of epothilone analogs and intermediates
INVENTOR(S): Li, Wen-Sen; Thornton, John E.; Guo, Zhenrong; Swaminathan, Shankar
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002060904	A2	20020808	WO 2002-US1853	20020122
WO 2002060904	A3	20030227		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 6518421	B1	20030211	US 2001-775361	20010201
US 2003004338	A1	20030102	US 2001-946721	20010905
AU 2002240014	A1	20020812	AU 2002-240014	20020122
PRIORITY APPLN. INFO.:			US 2001-775361	20010201
			US 2001-946721	20010905
			US 2000-528526	20000320
			WO 2002-US1853	20020122

OTHER SOURCE(S): MARPAT 137:140388

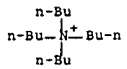
GI



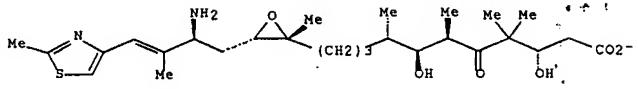
I

AB The present invention relates to a process for the preparation of epothilone analogs, such as I [RR1 = NH (II)], by initially forming novel ring-opened epothilones and carrying out a macrolactamization reaction thereon. The subject process is amenable to being carried out in a single reaction vessel without isolation of the intermediate compound and provides at least about a three-fold increase in yield over prior processes for preparing the desired epothilone analogs. Thus, ring opening of epothilone B was achieved using NaN3, PMe3 and Bu4NCl in THF in the presence of Pd2(dba)3.CHCl3 to form TBA salt I [R = NH2, R1 = O-.Bu4N+ (III)] in 93% yield. III underwent intramol. macrolactamization using K2CO3, HOBt, and EDCI in THF and DMF to form II in 92.7% % yield.

RX(2) OF 4 ...C ===> J

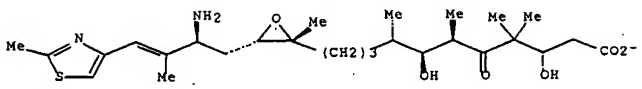


C: CM 1



C: CM 2

(2)



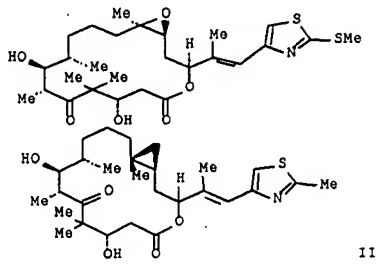
C: CM 2

(2)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(2) RCT C ***361204-09-3***
RGT K 584-08-7 K2CO3, L 2592-95-2 1-Benzotriazolol, M 25952-53-8 EDAP
PRO J ***219989-84-1***
SOL 109-99-9 THF, 68-12-2 DMF
CON SUBSTAGE(1) room temperature -> -5 deg C
SUBSTAGE(2) 5 minutes, -5 deg C
SUBSTAGE(3) 2 hours, -5 deg C
SUBSTAGE(4) 8 hours, 0 deg C
SUBSTAGE(5) 2 hours, 10 deg C
NTE optimization study
REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 6 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 137:310727 CASREACT Full-text
TITLE: Chemical synthesis and biological evaluation of novel epothilone B and trans-12,13-cyclopropyl epothilone B analogues
AUTHOR(S): Nicolaou, K. C.; Ritzen, Andreas; Namoto, Kenji; Buey, Ruben M.; Diaz, J. Fernando; Andreu, Jose M.; Wartmann, Markus; Altmann, Karl-Heinz; O'Brate, Aurora; Giannakakou, Paraskevi
CORPORATE SOURCE: Department of Chemistry and Skaggs Institute for Chemical Biology, Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Tetrahedron (2002), 58(32), 6413-6432
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

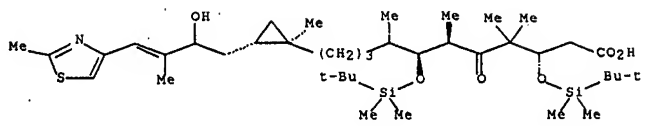


I

II

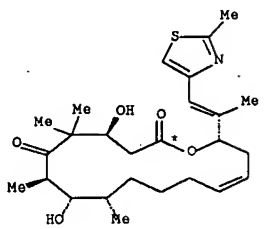
AB In addition to the total synthesis of the thiomethyl thiazole side chain analog of epothilone B I, a series of related trans-12,13-cyclopropyl epothilone B analogs, e.g. II, was accomplished. While the synthesis of the epothilone B analog I proceeded through a Stille coupling of a vinyl iodide substrate containing the epothilone macrocycle with the appropriate side chain stannane, that of the cyclopropyl analogs involved a convergent strategy in which a Nozaki-Hiyama-Kishi coupling was used as a means of introducing the side chains prior to Yamaguchi macrolactonization and final elaboration to the target mols. The synthesized analogs were subjected to biol. evaluation involving in vitro tubulin polymerization, affinity for the microtubule Taxol binding site and cell cytotoxicity assays. The results identified the methylthio thiazole side chain as a potency enhancing moiety for the epothilones and shed further light on the structure-activity relationships within this important class of chemotherapeutic agents.

RX(30) OF 782 ...***DH*** ===> ***I***...



DH

(30)



A
YIELD 45%

RX(3) RCT H ***514224-63-6***
PRO A ***186692-73-9***
CAT 252877-37-5 Synthase, epothilone
SOL 7732-18-5 Water, 67-68-5 DMSO
CON 22 hours, 30 deg C, pH 5
NTE biotransformation, enzymic, recombinant epothilone thioesterase domain used, phosphate-buffered soln., product distribution depends on reaction conditions
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

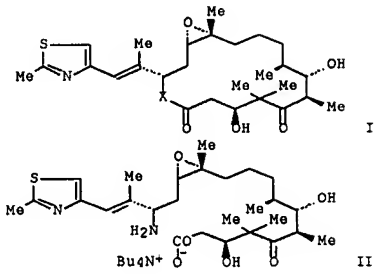
L90 ANSWER 5 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 138:153369 CASREACT Full-text
TITLE: Process for the preparation of epothilone analogs
INVENTOR(S): Li, Wen Sen; Thornton, John E.; Guo, Zhenrong; Swaminathan, Shankar
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: U.S., 17 pp., Cont.-in-part of U.S. Ser. No. 528,526.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6518421	B1	20030211	US 2001-775361	20010201
US 2003004338	A1	20030102	US 2001-946721	20010905
WO 2002060904	A2	20020808	WO 2002-US1853	20020122
WO 2002060904	A3	20030227		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2002240014	A1	20020812	AU 2002-240014	20020122
US 39356	E1	20061017	US 2005-56606	20050211
PRIORITY APPLN. INFO.:			US 2000-528526	20000320
			US 2001-775361	20010201
			US 2001-946721	20010905
			WO 2002-US1853	20020122

OTHER SOURCE(S): MARPAT 138:153369
GI

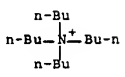


I

II

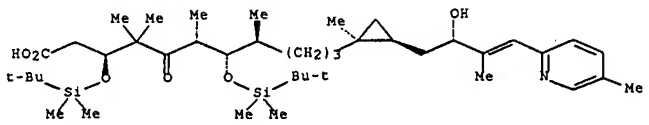
AB The present invention relates to a process for the preparation of epothilone analogs by initially forming novel ring-opened epothilones and carrying out a macrolactamization reaction thereon. The subject process is amenable to being carried out in a single reaction vessel without isolation of the intermediate compound and provides at least about a three-fold increase in yield over prior processes for preparing the desired epothilone analogs. Thus, epothilone B I (X = O) was treated with NaN3 and Bu4N+Cl- in THF followed by addition of water PMe3 in THF and equilibrated to 25° then addition of Pd2(dba)3.CHCl3. The resulting solution was stirred under an argon atmospheric for 19 h. to form ring opened salt II in 96% yield. Salt II was then dissolved in THF and DMF, cooled to -5°, treated with K2CO3 and stirred for 5 min before adding HOBt and EDCI then stirring for 2 h at -5° to form lactam I (X =NH) in 56% yield from epothilone B.

RX(2) OF 4 ...C ===> J



C: CM 1

RX(38) OF 219 ...DB ===> E...

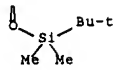


DB

(38)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

PAGE 2-A



E
YIELD 33%

RX(38) RCT DB 611168-66-2

STAGE(1)
RGT DJ 4136-95-2 2,4,6-Cl3C6H2COCl, BD 121-44-8 Et3N
SOL 109-99-9 THF
CON 1 hour, 0 deg C

STAGE(2)
RGT CF 1122-58-3 4-DMAP
SOL 108-88-3 PhMe
CON 3 hours, 75 deg C

PRO E 611168-68-4
NTE Yamaguchi reaction, addnl. stereoisomeric reactant present
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

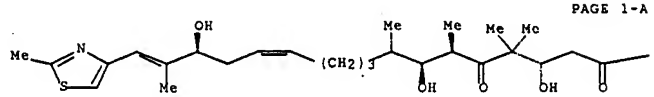
L90 ANSWER 4 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 138:316732 CASREACT Full-text
TITLE: Epothilone C Macrolactonization and Hydrolysis Are Catalyzed by the Isolated Thioesterase Domain of Epothilone Polyketide Synthase

AUTHOR(S): Boddy, Christopher N.; Schneider, Tanya L.; Hotta, Kinya; Walsh, Christopher T.; Khosla, Chaitan
CORPORATE SOURCE: Departments of Chemical Engineering, Chemistry and Biochemistry, Stanford University, Stanford, CA, 94305-5025, USA
SOURCE: Journal of the American Chemical Society (2003), 125(12), 3428-3429
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

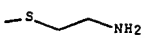
AB Epothilone C is produced by the combined action of one nonribosomal peptide synthetase (NRPS) and nine polyketide synthase (PKS) modules in a multienzyme system. The final step in the biosynthesis is the thioesterase (TE)-catalyzed cyclorelease of epothilone from the EpoF protein. It has been unclear whether isolated PKS TE domains could exhibit macrolactonization activity. Here we demonstrate that the excised epothilone TE domain can catalyze the efficient cyclization of the N-acetylcysteamine thioester of seco-epothilone C to generate epothilone C (kcat/KM = 0.41 ± 0.03 min-1 mM-1). The TE domain also catalyzes the hydrolysis of both the N-acetylcysteamine thioester of seco-epothilone C (kcat = 0.087 ± 0.005 min-1, KM = 291 ± 53 μM) and that of the epothilone C (kcat = 0.67 ± 0.01 min-1, KM = 117 ± 5 μM) to form seco-epothilone C.

RX(3) OF 8 ...H ===> A...

PAGE 1-A



PAGE 1-B



H

(3)

CON 1 hour, room temperature

STAGE(5)
SOL 60-29-7 Et2O, 75-09-2 CH2Cl2
CON room temperature

STAGE(6)
SOL 7732-18-5 Water
CON room temperature

STAGE(7)
SOL 109-99-9 THF
CON room temperature -> -5 deg C

STAGE(8)
RGT CA 121-44-8 Et3N
CON -5 deg C

STAGE(9)
RGT CB 4136-95-2 2,4,6-Cl3C6H2COCl
CON SUBSTAGE(1) -5 deg C
SUBSTAGE(2) -5 deg C -> 0 deg C
SUBSTAGE(3) 1 hour, 0 deg C

STAGE(10)
RGT CC 1122-58-3 4-DMAP
SOL 108-88-3 PhMe
CON 4 hours, room temperature

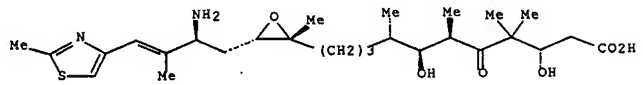
PRO BW ***867376-54-3***, BX ***867376-57-6***
NTE sixth stage quench
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 2 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 143:211773 CASREACT Full-text
TITLE: Method for synthesis of Epothilon B lactam derivative
INVENTOR(S): Yan, Jialin
PATENT ASSIGNEE(S): Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, No pp. given
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1554659	A	20041215	CN 2003-10112901	20031225
PRIORITY APPLN. INFO.:			CN 2003-10112901	20031225

AB Epothilon B lactam derivative was synthesized from Epothilone B via regional and stereo selective nitridization of the Epsilon B macrolide catalyzed by palladium tri-Ph phosphine. Epothilone B was first ring opened via nitridization reaction to obtain nitronic acid, then processed with tri-Ph phosphine to produce imino phosphorane, later hydrolyzed with ammonium hydroxide to form amino acid, and finally the amino acid was cyclized with DPPA and solid sodium bicarbonate to obtain the target product Epothilone B lactam derivative

RX(3) OF 6 ...G ===> J



G

(3)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(3) RCT G ***219990-25-7***
RGT K 144-55-8 NaHCO3, L 26386-88-9 (PhO)2P(O)N3
PRO J ***219989-84-1***
SOL 68-12-2 DMF
CON 24 hours, 4 deg C

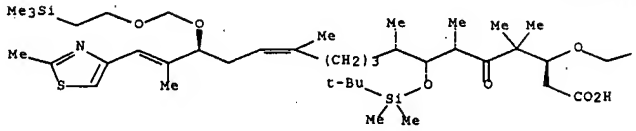
L90 ANSWER 3 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 139:301287 CASREACT Full-text
TITLE: Design, synthesis, and biological properties of highly potent epothilone B analogues
AUTHOR(S): Nicolaou, K. C.; Sasmal, Pradip K.; Rassias, Gerasimos; Reddy, Mali Venkat; Altmann, Karl-Heinz; Wartmann, Markus; O'Brate, Aurora; Giannakakou, Paraskevi
CORPORATE SOURCE: Department of Chemistry, The Skaggs Institute for Chemical Biology The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Angewandte Chemie, International Edition (2003), 42(30), 3515-3520
CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Epothilones have potent cytotoxicity against tumor cells. We directed our attention toward the synthesis and evaluation of a small designed library of epothilone B analogs. From the library, we found that 12,13-cis-cyclopropane methylsulfanyl epothilone B is extremely potent.

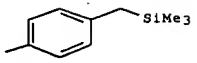
(TBDMS = SiMe2CMe3) was prepared from camphosultam V via protection with novel reagent, 4-[(trimethylsilyl)methyl]benzyl trichloroacetimidate, basic hydrolysi with LiOH in aqueous THF, stereoselective aldol reaction with undecadienal VI in THF containing LDA, silylation with CF3SO2SiMe2CMe3 in CH2Cl2 containing 2,6-lutidine and regioselective desilylation with MgBr2 in Et2O;MeNO2 containing BuSH, and macrolactonization with 2,4,6-Cl3C6H2COCl in THF containing Et3N followed by DMAP in PhMe.

RX(28) OF 58 ...***BQ*** + ***BR*** ===> ***BW*** + ***BX***

PAGE 1-A

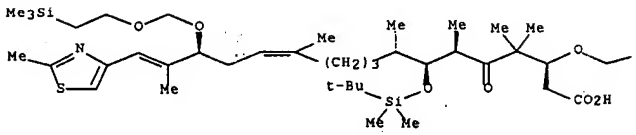


PAGE 1-B

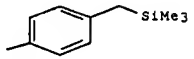


BQ

PAGE 1-A



PAGE 1-B



BR

(28)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

PAGE 2-A

BW
YIELD 17%

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

PAGE 2-A

BX
YIELD 33%

RX(28)

STAGE(1)
RGT BY 7789-48-2 MgBr2
SOL 60-29-7 Et2O
CON room temperature

STAGE(2)
SOL 75-52-5 MeNO2
CON room temperature

STAGE(3)
RGT BZ 109-79-5 BuSH
CON room temperature

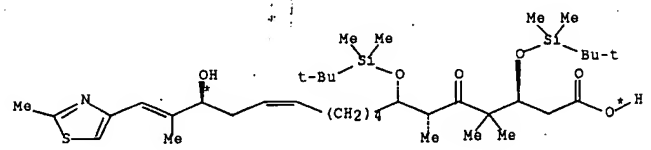
STAGE(4)
RCT BQ ***867376-53-2***, BR ***867376-58-7***
SOL 60-29-7 Et2O

STAGE(2)
RGT Z 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

PRO AH ***240816-03-9***
NTE key step
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 7 OF 7 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: ***127:108793*** CASREACT Full-text
TITLE: Stereoselective syntheses and evaluation of compounds in the 8-desmethylepothilone A series: some surprising observations regarding their chemical and biological properties
AUTHOR(S): Balog, Aaron; Betinato, Peter; Su, Dai-Shi; Meng, Dongfang; Sorensen, Erik; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.
CORPORATE SOURCE: Lab. Bioorganic Chem., Sloan-Kettering Inst. Cancer Res., New York, NY, 10021, USA
SOURCE: Tetrahedron Letters (1997), 38(26), 4529-4532
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The title compds. have been synthesized in a convergent way by recourse to a Weiler type dianion construction.

RX(3) OF 15 ...I ===> !`L...



I

(3)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(3) RCT I ***192370-80-2***
RGT M 538-75-0 DCC, N 1122-58-3 4-DMAP
PRO L ***192370-81-3***
SOL 67-66-3 CHCl3
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 1 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 143:422202 CASREACT Full-text
TITLE: Novel protecting reagents, protecting groups and methods of forming and using the same
INVENTOR(S): Avery, Mitchell A.; Chittiboyina, Amar Gopal; Chada, Raji Reddy; Kache, Rajashaker; Jung, Jae Chul
PATENT ASSIGNEE(S): The University of Mississippi, USA
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005100329	A1	20051027	WO 2005-US9525	20050323

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-555896P 20040323
OTHER SOURCE(S): MARPAT 143:422202
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

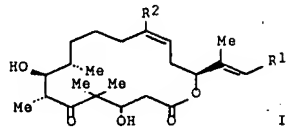
AB New protecting reagents TIX-Y (Y = OCNHCCl3, Cl, Br, I, NCO, OCOCl, OCH2Cl, OTs, OMs, ONs, OTf) are provided that allow for the selective placement of a new protecting group onto a reactive site of a multifunctional compound The TIX-Y reagents are 2, 3, and 4-trialkylsilylxylyl, triarylsilylxylyl or a combination of alkyl-aryl silylxylyl reagents [TIX reagents, I (R, R'', R''' = alkyl, aryl), II (R, R'', R''' = alkyl, aryl) and III (R, R'', R''' = alkyl, aryl)], which carry a TIX protecting group for protecting alcs. as ethers, urethanes, carbonates, acetals; amines as carbamates or ureas; and thiols as ethers or esters. The invention also provides methods of forming the 2, 3, and 4-TIX reagents; introducing the TIX protecting groups to mols. bearing hydroxyl groups, amine groups, or thiol groups; methods of removing the TIX protecting groups; and intermediate compds. formed during any one of these methods. The invention further provides methods useful in producing epothilones and analogs and derivs. thereof. Thus, epothilone derivative IV

STAGE(1)
RGT X 4136-95-2 2,4,6-Cl3C6H2COCl, O 121-44-8 Et3N
SOL 109-99-9 THF

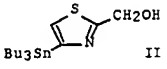
STAGE(2)
RGT Y 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

PRO W ***226940-49-4***
NTE key step

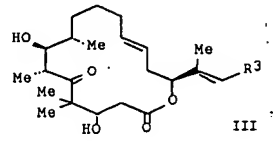
L109 ANSWER 6 OF 7 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: ***131:199535*** CASREACT Full-text
TITLE: Total synthesis of epothilone E and related side-chain modified analogues via a Stille coupling based strategy
AUTHOR(S): Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninkovic, S.; Hepworth, D.
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Bioorganic & Medicinal Chemistry (1999), 7(5), 665-697
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



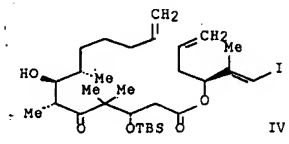
I



II



III

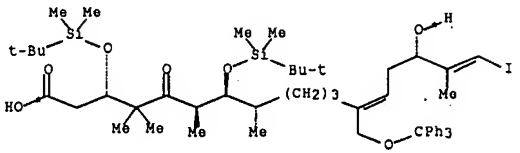


IV

AB A Stille coupling strategy has been utilized to complete a total synthesis of epothilone E from vinyl iodide I (R1 = I; R2 = H) and thiazolestannane II. The central core fragment I (R1 = I; R2 = H) and its trans-isomer III (R3 = I) were prepared from triene IV (TBS = SiMe2CMe3) using ring-closing metathesis (RCM), and were subsequently coupled to a variety of alternative stannanes to

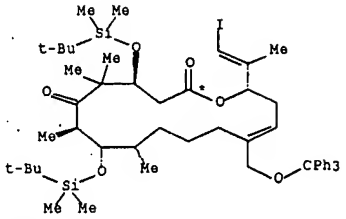
provide a library of epothilone analogs I [R1 = 2-(5-acetoxypentyl)thiazol-4-yl, 2-(methylthio)thiazol-4-yl, 2-piperidinothiazol-4-yl, 2-methoxythiazol-4-yl, 2-ethoxythiazol-4-yl, thiazol-4-yl, thiazol-2-yl, thiazol-5-yl, 2-(hydroxymethyl)thiazol-4-yl, 2-(acetoxymethyl)thiazol-4-yl, 2-(fluoromethyl)thiazol-4-yl, 2-vinylthiazol-4-yl, 2-ethylthiazol-4-yl, 2-furyl, 2-thienyl, Ph,3-pyridyl, CH:C(OEt)Me-(Z), R2 = H] and III [R3 = 2-(5-acetoxypentyl)thiazol-4-yl, 2-(methylthio)thiazol-4-yl, 2-piperidinothiazol-4-yl, 2-methoxythiazol-4-yl, 2-ethoxythiazol-4-yl, thiazol-4-yl, thiazol-2-yl, thiazol-5-yl, 2-(hydroxymethyl)thiazol-4-yl, 2-(acetoxymethyl)thiazol-4-yl, 2-(fluoromethyl)thiazol-4-yl, 2-vinylthiazol-4-yl, 2-ethylthiazol-4-yl, 2-furyl, 2-thienyl, Ph,3-pyridyl, CH:C(OEt)Me-(Z)]. The Stille coupling approach was then used to prepare epothilone B analogs from the key macrolactone intermediate I (R1 = I, R2 = CH2OH) which was itself synthesized by a macrolactonization based strategy.

RX(19) OF 264 ...***BT*** ===> ***AH***...



BT

(19) →

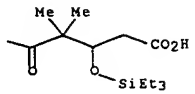


AH
YIELD 84%

RX(19) RCT BT ***240816-02-8***

STAGE(1)
RGT CB 4136-95-2 2,4,6-Cl3C6H2COCl, BW 121-44-8 Et3N
SOL 109-99-9 THF

PAGE 1-B



AY

(12)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(12) RCT AY ***298702-20-2***

STAGE(1)
RGT N 121-44-8 Et3N, BB 50-43-1 Benzoic acid, 2,4,6-trichloro-
SOL 109-99-9 THF

STAGE(2)
RGT BC 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

PRO BA ***298702-21-3***
NTE STEREOSELECTIVE

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 5 OF 7 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: ***132:49832*** CASREACT Full-text
TITLE: Preparation of 16-desmethylepothilones for the treatment of proliferative diseases.
INVENTOR(S): Nicolaou, Kyriacos Costa; Hepworth, David; Finlay, Maurice Raymond Verschoyle; King, Nigel Paul
PATENT ASSIGNEE(S): Novartis A.-G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.; Scripps Research Institute
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9967253	A2	19991229	WO 1999-EP4299	19990621
WO 9967253	A3	20000420		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,

DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6380394	B1	20020430	US 1998-102602	19980622
AU 9947752	A	20000110	AU 1999-47752	19990621
PRIORITY APPLN. INFO.:			US 1998-102602	19980622
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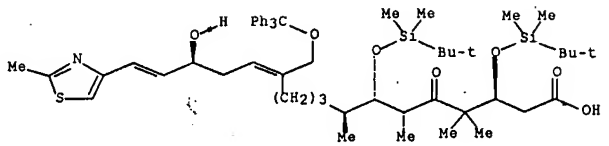
			US 1999-124653P	19990316
			US 1996-32864P	19961213
			US 1997-856533	19970514
			US 1997-923869	19970904
			WO 1999-EP4299	19990621

OTHER SOURCE(S): MARPAT 132:49832
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to compds. I [X = bond, O; Q = OH, I, H], and methods of synthesis of I, as well as for the synthesis of epothilone B (II) and their intermediates. Thus, 16-desmethyldesoxyepothilone analog III was prepared via Yamaguchi macrolactonization of hydroxy acid IV. The compds. I can be used e.g. in the treatment of proliferative diseases.

RX(4) OF 46 ...*J* ===> ***W***...



J

(4)

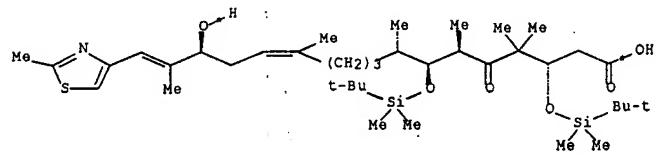
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(4) RCT J ***252986-91-7***

NTE STEREOSELECTIVE
REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 3 OF 7 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: ***134:4795*** CASREACT Full-text
TITLE: Total Syntheses of Epothilones B and D
AUTHOR(S): Mulzer, Johann; Mantoulidis, Andreas; Oehler, Elisabeth
CORPORATE SOURCE: Institut fuer Organische Chemie, Universitaet Wien, Vienna, A-1090, Austria
SOURCE: Journal of Organic Chemistry (2000), 65(22), 7456-7467 CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Total syntheses of the microtubule stabilizing antitumor drugs epothilone B and D are described, starting from optically pure (S)-malic acid and Me (R)-3-hydroxy-2-methylpropionate. The synthesis is highly convergent by coupling the three fragments C1-C6 (fragment D), C7-C10 (fragment C), and C11-C21 (fragment B). Key steps are two stereoselective Wittig type olefinations to generate the 12,13- and 16,17-double bonds, an enantioselective Mukaiyama aldol addition to synthesize fragment D, and a sulfone anion allyl iodide alkylation to connect fragments B and C. Finally fragment D was attached to the B + C fragment via aldol addition

RX(34) OF 711 ...***DL*** ===> ***H***...



DL

(34)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(34) RCT DL ***193146-26-8***

STAGE(1)
RGT DN 1122-58-3 4-DMAP, DO 25952-53-8 EDAP, DP 71561-71-2

4-Me2NC5H4N.HCl
SOL 67-66-3 CHCl3

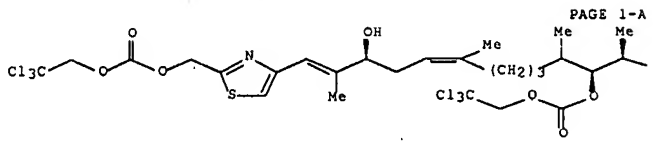
STAGE(2)
RGT AK 12125-02-9 NH4Cl
SOL 7732-18-5 Water

PRO H ***189453-35-8***
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 4 OF 7 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: ***133:266634*** CASREACT Full-text
TITLE: Total Synthesis and Antitumor Activity of 12,13-Desoxyepothilone F: An Unexpected Solvolysis Problem at C15, Mediated by Remote Substitution at C21
AUTHOR(S): Lee, Chul Bom; Chou, Ting-Chao; Zhang, Xiu-Guo; Wang, Zhi-Guang; Kuduk, Scott D.; Chappell, Mark D.; Stachel, Shawn J.; Danishefsky, Samuel J.
CORPORATE SOURCE: Laboratory for Bioorganic Chemistry, The Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, USA
SOURCE: Journal of Organic Chemistry (2000), 65(20), 6525-6533 CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A new epothilone analog, 12,13-desoxyepothilone F (dEpoF, 21-hydroxy-12,13-desoxyepothilone B, 21-hydroxyepothilone D), was synthesized and evaluated for antitumor potential. A convergent strategy employed for the semi-practical synthesis of 12,13-desoxyepothilone B (dEpoB) has been utilized to yield an amount of dEpoF sufficient for relevant biol. studies. The results from an in vitro assay reveal that this new analog is highly active against various tumor cell lines with a potency comparable to that of dEpoB. In particular, the growth of resistant tumor cells is inhibited by dEpoF at concns. where paclitaxel (Taxol) is basically ineffective. A preliminary assessment of its in vivo activity is also promising. The new analog, containing an addnl. hydroxyl group at C21, exhibits advantages over other epothilones in terms of water solubility, and can serve as a readily functionalizable handle to produce other useful compds. for pertinent biol. studies.

RX(12) OF 128 ...***AY*** ===> ***BA***...

PAGE 1-A



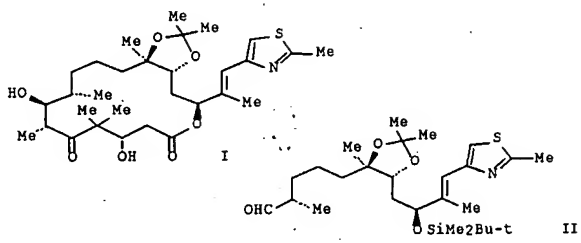
STAGE(2)
SOL 108-88-3 PhMe

STAGE(3)
RGT AV 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

PRO W *279226-97-0*
NTE stereoselective

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 2 OF 7 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: *134:29228* CASREACT Full-text
TITLE: A novel highly stereoselective total synthesis of epothilone B and of its (12R,13R) acetonide
AUTHOR(S): Mulzer, J.; Karig, G.; Pojarliev, P.
CORPORATE SOURCE: Institut fur Organische Chemie der Universitat Wien, Vienna, A-1090, Austria
SOURCE: Tetrahedron Letters (2000), 41(40), 7635-7638
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

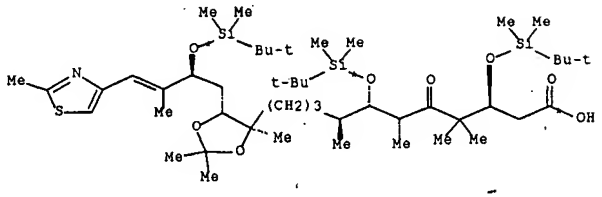


I

II

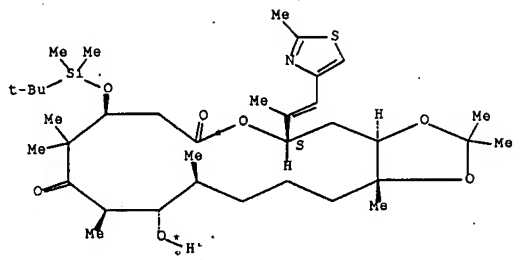
AB Stereoselective syntheses of epothilone B and its novel derivative I are described. Key steps are the formation of intermediate II via Sharpless AD-reaction and Davis-Evans-hydroxylation.

RX(30) OF 447 ...*CI* ===> *CM*...



CI

(30)



CM
YIELD 50%

RX(30) RCT CI *312492-96-9*

STAGE(1)
RGT CN 429-41-4 Bu4N.F
SOL 109-99-9 THF

STAGE(2)
RGT CO 4136-95-2 2,4,6-Cl3C6H2COCl, AF 121-44-8 Et3N
SOL 108-88-3 PhMe

STAGE(3)
RGT CP 1122-58-3 4-DMAP
SOL 108-88-3 PhMe

PRO CM *312492-98-1*

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L109 7 SEA FILE=CASREACT ABB=ON PLU=ON L108 NOT L90

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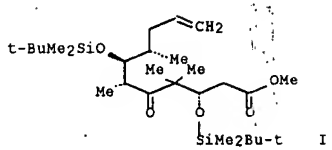
L109 ANSWER 1 OF 7 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: ***134:178371*** CASREACT Full-text
TITLE: Synthesis and biological evaluation of highly potent analogues of epothilones B and D
AUTHOR(S): Altmann, K.-H.; Bold, G.; Caravatti, G.; Florsheimer, A.; Guagnano, V.; Wartmann, M.
CORPORATE SOURCE: Novartis Pharma AG, TA Oncology Research, Basel, CH-4002, Switz.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(24), 2765-2768
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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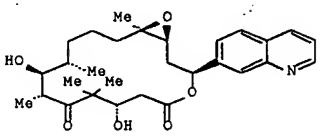
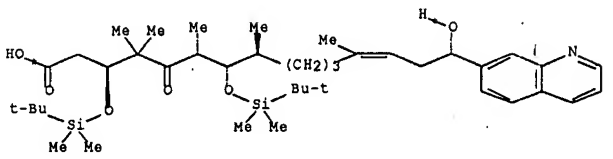


II

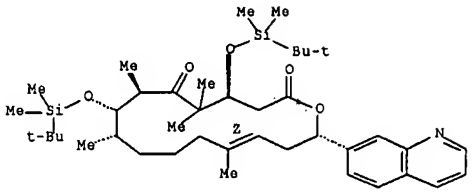
AB A series of new epothilone B and D analogs incorporating fused hetero-aromatic side chains have been prepared The synthetic strategy is based on olefin I as the common intermediate and allows variation of the side-chain structure in a highly convergent and stereoselective manner. These epothilone analogs, e.g. II, are more potent inhibitors of cancer cell proliferation than the corresponding parent epothilones B or D.

RX(11) OF 370 ...**AR** ===> **W**...



AR

(11)



W
YIELD 70%

RX(11) RCT AR ***279226-96-9***

STAGE(1)
RGT . AT 4136-95-2 2,4,6-Cl3C6H2COCl, AU 121-44-8 Et3N
SOL 109-99-9 THF

```
chain nodes :
12  13  14  15  16  17  18  19  20  21  22
ring/chain nodes :
1  2  3  4  5  6  7  8  9  10  11
chain bonds :
2-12  2-13  3-14  3-15  4-16  4-17  6-18  8-19  10-20  11-21  11-22
ring/chain bonds :
1-2  2-3  3-4  4-5  5-6  6-7  7-8  8-9  9-10  10-11
exact/norm bonds :
1-2  2-3  3-4  4-5  5-6  6-7  6-18  7-8  8-9  8-19  9-10  10-11
exact bonds :
2-12  2-13  3-14  3-15  4-16  4-17  10-20  11-21  11-22


Match level :
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10:CLASS  11:CLASS  12:CLASS  13:CLASS  14:CLASS  15:CLASS  16:CLASS  17:CLASS
18:CLASS  19:CLASS
20:CLASS  21:CLASS  22:CLASS



L3          560 SEA FILE=REGISTRY SSS FUL L1
L34       22933 SEA FILE=REGISTRY ABB=ON  PLU=ON  OC15/ESS
L35       27330 SEA FILE=REGISTRY ABB=ON  PLU=ON  C16/ESS
L36         726 SEA FILE=REGISTRY ABB=ON  PLU=ON  NC15/ESS
L37           0 SEA FILE=REGISTRY ABB=ON  PLU=ON  NSC14/ESS
L38       50989 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L34 OR L35 OR L36 OR L37)
L39       12165 SEA FILE=REGISTRY ABB=ON  PLU=ON  L38 AND CASREACT/LC
L40        2534 SEA FILE=CASREACT ABB=ON  PLU=ON  L39/PRO
L42          65 SEA FILE=CASREACT ABB=ON  PLU=ON  L3/RRT
L43          59 SEA FILE=CASREACT ABB=ON  PLU=ON  L42 (L) L40
L85          59 SEA FILE=CASREACT ABB=ON  PLU=ON  L43 (L) 1/NS
L88          31 SEA FILE=CASREACT ABB=ON  PLU=ON  L43 (L) 4/NS
L90          28 SEA FILE=CASREACT ABB=ON  PLU=ON  L85 NOT L88


=>

=> => d stat que L109
L1              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation:
Uploading L1.str
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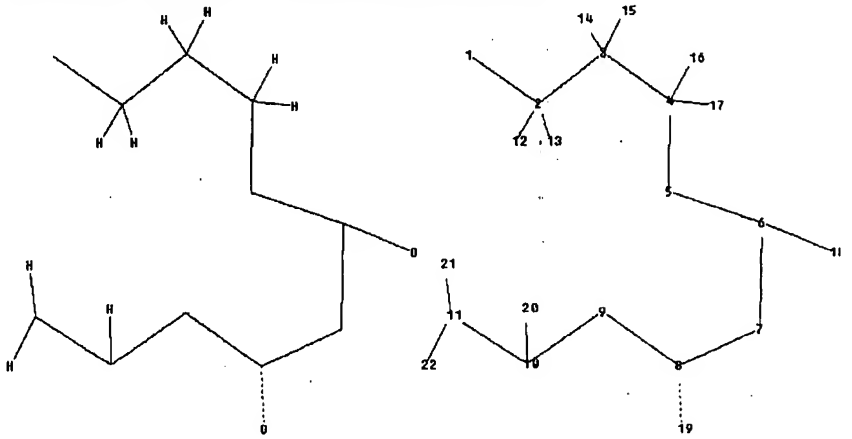


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chain nodes :
12  13  14  15  16  17  18  19  20  21  22
ring/chain nodes :
1  2  3  4  5  6  7  8  9  10  11
chain bonds :
2-12  2-13  3-14  3-15  4-16  4-17  6-18  8-19  10-20  11-21  11-22
ring/chain bonds :
1-2  2-3  3-4  4-5  5-6  6-7  7-8  8-9  9-10  10-11
exact/norm bonds :
1-2  2-3  3-4  4-5  5-6  6-7  6-18  7-8  8-9  8-19  9-10  10-11
exact bonds :
2-12  2-13  3-14  3-15  4-16  4-17  10-20  11-21  11-22


Match level :
1:CLASS  2:CLASS  3:CLASS  4:CLASS  5:CLASS  6:CLASS  7:CLASS  8:CLASS  9:CLASS
10:CLASS  11:CLASS  12:CLASS  13:CLASS  14:CLASS  15:CLASS  16:CLASS  17:CLASS
18:CLASS  19:CLASS
20:CLASS  21:CLASS  22:CLASS



L3          560 SEA FILE=REGISTRY SSS FUL L1
L34       22933 SEA FILE=REGISTRY ABB=ON  PLU=ON  OC15/ESS
L35       27330 SEA FILE=REGISTRY ABB=ON  PLU=ON  C16/ESS
L36         726 SEA FILE=REGISTRY ABB=ON  PLU=ON  NC15/ESS
L37           0 SEA FILE=REGISTRY ABB=ON  PLU=ON  NSC14/ESS
L38       50989 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L34 OR L35 OR L36 OR L37)
L39       12165 SEA FILE=REGISTRY ABB=ON  PLU=ON  L38 AND CASREACT/LC
L40        2534 SEA FILE=CASREACT ABB=ON  PLU=ON  L39/PRO
L42          65 SEA FILE=CASREACT ABB=ON  PLU=ON  L3/RRT
L43          59 SEA FILE=CASREACT ABB=ON  PLU=ON  L42 (L) L40
L85          59 SEA FILE=CASREACT ABB=ON  PLU=ON  L43 (L) 1/NS
L88          31 SEA FILE=CASREACT ABB=ON  PLU=ON  L43 (L) 4/NS
```

```
            STAGE(1)
               RGT  AW 1191-15-7 AlH(Bu-i)2
               SOL  108-88-3 PhMe

            STAGE(2)
               RGT  BK 7647-01-0 HCl
               SOL  7732-18-5 Water, 67-56-1 MeOH

          PRO  BJ 226940-68-7

RX(16)    RCT  BL 187527-25-9

            STAGE(1)
               RGT  BE 108-18-9 i-Pr2NH, BF 109-72-8 BuLi
               SOL  109-99-9 THF, 110-54-3 Hexane

            STAGE(2)
               RCT  BJ 226940-68-7
               SOL  109-99-9 THF

            STAGE(3)
               RGT  BO 64-19-7 AcOH
               SOL  109-99-9 THF

          PRO  BM 240815-96-7, BN 240815-97-8
REFERENCE COUNT:          60    THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
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=> file casreact
FILE 'CASREACT' ENTERED AT 12:18:14 ON 11 OCT 2007
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FILE CONTENT:1840 - 6 Oct 2007 VOL 147 ISS 16

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*************************************************************
*                                                           *
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*                                                           *
*************************************************************

Some CASREACT records are derived from the ZIC/VINITI database (1974-1999)
provided by InfoChem, INPI data prior to 1986, and Biotransformations
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This file contains CAS Registry Numbers for easy and accurate substance
identification.

=> d stat que L90
L1              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation:
Uploading L1.str
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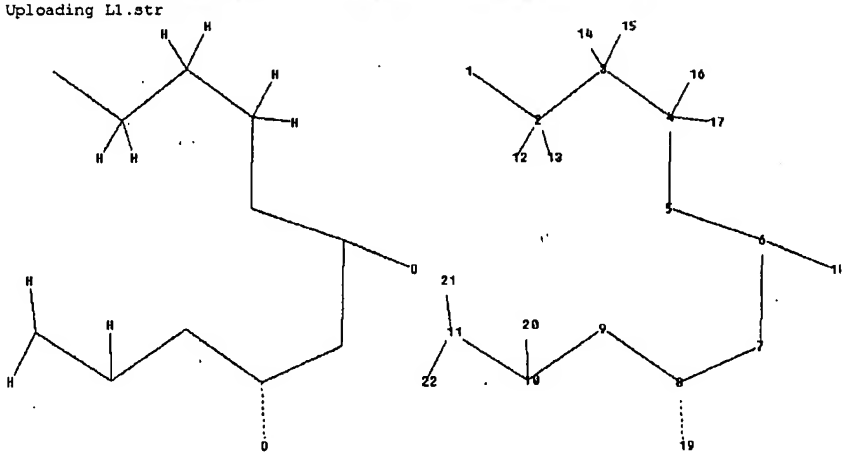

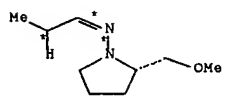

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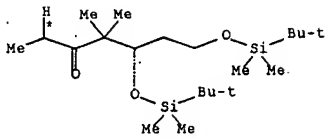
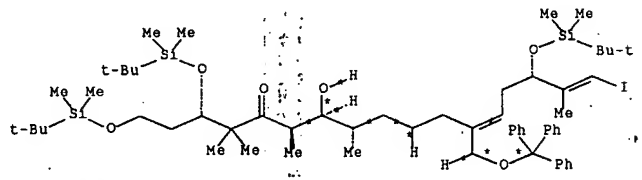
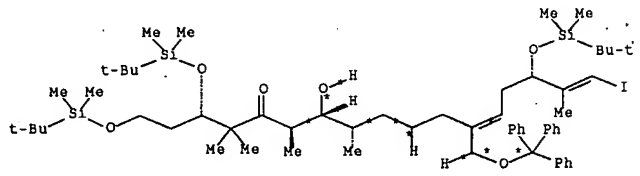


2 BL

7
STEPS



BM
YIELD 39%



BN
YIELD 27%

RX(10) RCT AK ***226940-62-1***, AR 95561-65-2
PRO AS 240815-89-8
SOL 71-43-2 Benzene

RX(11) RCT AS 240815-89-8

STAGE(1)
RGT AW 1191-15-7 AlH(Bu-i)2
SOL 109-99-9 THF, 75-09-2 CH2Cl2

STAGE(2)
RCT AU 76-83-5
RGT Z 1122-58-3 4-DMAP
SOL 68-12-2 DMF

PRO AV 240815-91-2

RX(12) RCT AV 240815-91-2

STAGE(1)
RGT AY 280-64-8 9-BBN
SOL 109-99-9 THF

STAGE(2)
RGT AZ 1310-73-2 NaOH, D 7722-84-1 H2O2
SOL 7732-18-5 Water

STAGE(3)
RGT AL 288-32-4 1H-Imidazole, BA 603-35-0 PPh3
SOL 60-29-7 Et2O, 75-05-8 MeCN

STAGE(4)
RGT BB 7553-56-2 I2

PRO AX 240815-93-4
NTE (95%;97%)

RX(13) RCT BC 70113-32-5

STAGE(1)
RGT BE 108-18-9 i-Pr2NH, BF 109-72-8 BuLi
SOL 109-99-9 THF, 110-54-3 Hexane

STAGE(2)
RCT AX 240815-93-4
SOL 109-99-9 THF

PRO BD 240815-94-5
NTE stereoselective

RX(14) RCT BD 240815-94-5
RGT BI 109536-69-8 2-HO2CC6H4CO3H.Mg
PRO BH 240815-95-6
SOL 7732-18-5 Water, 67-56-1 MeOH, 109-99-9 THF
NTE phosphate buffer (7.0)

RX(15) RCT BH 240815-95-6

CAT 3144-16-9 10-CSA
SOL 67-56-1 MeOH, 75-09-2 CH2Cl2

STAGE(2)
RGT H 87413-09-0 Martin's reagent
SOL 75-09-2 CH2Cl2

PRO AN 193146-27-9
NTE (82%;97%)

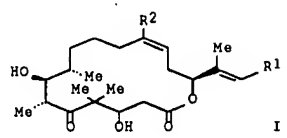
RX(22) RCT V 185148-95-2

STAGE(1)
RGT X 109-72-8 BuLi, Y 108-18-9 i-Pr2NH
SOL 109-99-9 THF, 110-54-3 Hexane

STAGE(2)
RCT AN 193146-27-9
SOL 109-99-9 THF

PRO BY ***210690-87-2***, BZ 250284-01-6
NTE stereoselective key step
REFERENCE COUNT: 82 THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 23 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 131:199535 CASREACT Full-text
TITLE: Total synthesis of epothilone E and related side-chain modified analogues via a Stille coupling based strategy
AUTHOR(S): Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninkovic, S.; Hepworth, D.
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Bioorganic & Medicinal Chemistry (1999), 7(5), 665-697
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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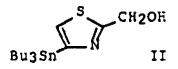

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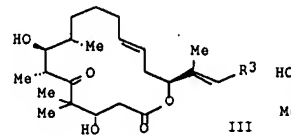

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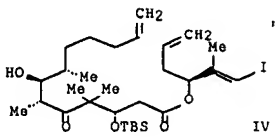
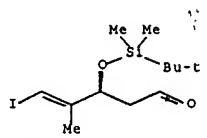


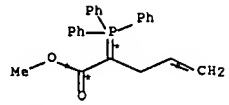
IV

AB A Stille coupling strategy has been utilized to complete a total synthesis of epothilone E from vinyl iodide I (R1 = I; R2 = H) and thiazolestannane II. The central core fragment I (R1 = I; R2 = H) and its trans-isomer III (R3 = I) were prepared from triene IV (TBS = SiMe2CMe3) using ring-closing metathesis (RCM), and were subsequently coupled to a variety of alternative stannanes to provide a library of epothilone analogs I [R1 = 2-(5-acetoxypentyl)thiazol-4-yl, 2-(methylthio)thiazol-4-yl, 2-piperidinothiazol-4-yl, 2-methoxythiazol-4-yl, 2-ethoxythiazol-4-yl, thiazol-4-yl, thiazol-2-yl, thiazol-5-yl, 2-(hydroxymethyl)thiazol-4-yl, 2-(acetoxymethyl)thiazol-4-yl, 2-(fluoromethyl)thiazol-4-yl, 2-vinylthiazol-4-yl, 2-ethylthiazol-4-yl, 2-furyl, 2-thienyl, Ph,3-pyridyl, CH:C(OEt)Me-(Z), R2 = H] and III [R3 = 2-(5-acetoxypentyl)thiazol-4-yl, 2-(methylthio)thiazol-4-yl, 2-piperidinothiazol-4-yl, 2-methoxythiazol-4-yl, 2-ethoxythiazol-4-yl, thiazol-4-yl, thiazol-2-yl, thiazol-5-yl, 2-(hydroxymethyl)thiazol-4-yl, 2-(acetoxymethyl)thiazol-4-yl, 2-(fluoromethyl)thiazol-4-yl, 2-vinylthiazol-4-yl, 2-ethylthiazol-4-yl, 2-furyl, 2-thienyl, Ph,3-pyridyl, CH:C(OEt)Me-(Z)]. The Stille coupling approach was then used to prepare epothilone B analogs from the key macrolactone intermediate I (R1 = I, R2 = CH2OH) which was itself synthesized by a macrolactonization based strategy.

RX(132) OF 264 COMPOSED OF RX(10), RX(11), RX(12), RX(13), RX(14), RX(15), RX(16)
RX(132) 2 ***AK*** + 2 AR + 2 AU + 2 BC + 2 BL ===> ***BM*** + BN

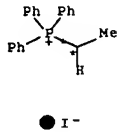


2 AK

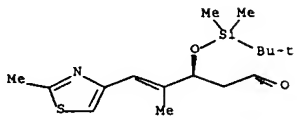


2 AR

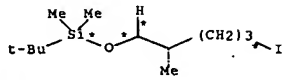
2 AU



2 AT



2 AU



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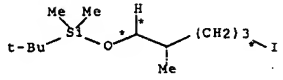

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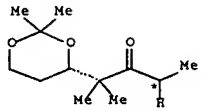
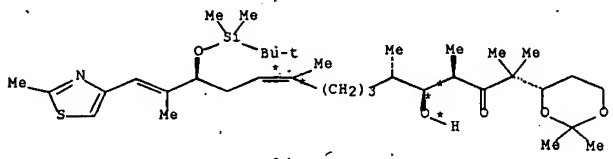
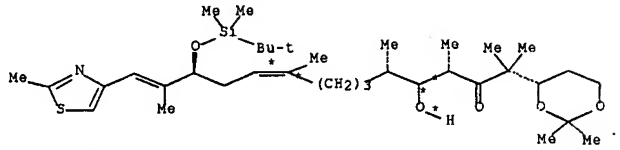


2 V

4 STEPS



BY
YIELD 82%



BZ
YIELD 9%

RX(12) RCT AT 4736-60-1

STAGE(1)
RGT X 109-72-8 BuLi
SOL 109-99-9 THF, 110-54-3 Hexane

STAGE(2)
RGT AW 7553-56-2 I2
SOL 109-99-9 THF

STAGE(3)
RGT U 1070-89-9 (Me3Si)2N.Na
SOL 109-99-9 THF

STAGE(4)
RCT AU ***188730-08-7***
SOL 109-99-9 THF

PRO AV 210690-66-7

RX(21) RCT AP 113453-27-3

STAGE(1)
RGT BS 12621-78-2 Zinc alloy, base, Zn,Cu
CAT 106-93-4 BrCH2CH2Br
SOL 71-43-2 Benzene

STAGE(2)
RGT Q 75-77-4 Me3SiCl, BT 127-19-5 AcNMe2

STAGE(3)
RGT BU 79271-56-0 F3CSO3SiEt3, BT 127-19-5 AcNMe2
CAT 14221-01-3 Pd(PPh3)4

STAGE(4)
RCT AV 210690-66-7
SOL 71-43-2 Benzene

PRO AM 210690-85-0
NTE key step

RX(10) RCT AM 210690-85-0

STAGE(1)

STAGE(5)
SOL 109-66-0 Pentane

PRO B 298702-07-5
NTE STEREOSELECTIVE

RX(1) RCT A 224580-52-3

STAGE(1)
RGT D 280-64-8 9-BBN
SOL 109-99-9 THF

STAGE(2)
RCT B 298702-07-5
RGT E 534-17-8 Cs2CO3, F 603-32-7 Ph3As
CAT 72287-26-4 Palladium, [1,1'-bis(diphenylphosphino-κP)ferrocene]dichloro-, (SP-4-2)-
SOL 68-12-2 DMF

STAGE(3)
SOL 7732-18-5 Water

PRO C 298702-16-6
NTE STEREOSELECTIVE

RX(9) RCT C 298702-16-6

STAGE(1)
RGT AR 7647-01-0 HCl
SOL 67-56-1 MeOH

STAGE(2)
RGT O 144-55-8 NaHCO3
SOL 7732-18-5 Water

STAGE(3)
SOL 75-09-2 CH2Cl2

PRO AQ 298702-17-7
NTE STEREOSELECTIVE

RX(10) RCT AQ 298702-17-7, AS 67-56-1

STAGE(1)
RGT AV 1333-74-0 H2
CAT 109361-17-3 Ruthenium, bis[(1R)-[1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine-κP]]di-μ-chlorodichloro(N,N-diethylethanamine)di-
SOL 67-56-1 MeOH

STAGE(2)
RGT O 144-55-8 NaHCO3

STAGE(3)
SOL 75-09-2 CH2Cl2

PRO AT ***298702-18-8***, AU 298702-19-9
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 22 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 131:351125 CASREACT Full-text
TITLE: Syntheses of (-)-epothilone B
AUTHOR(S): Schinzer, Dieter; Bauer, Armin; Schieber, Jennifer
CORPORATE SOURCE: Chemisches Institut der Otto-von-Guericke-Universitat, Magdeburg, D-39106, Germany
SOURCE: Chemistry--A European Journal (1999), 5(9), 2492-2500
CODEN: CEUJED; ISSN: 0947-6539
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
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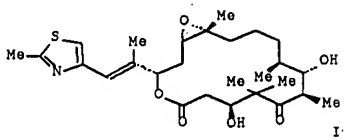

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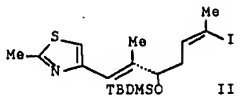


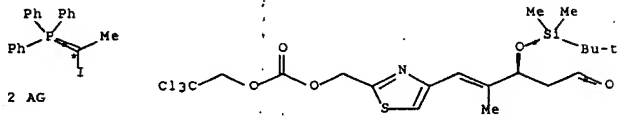
II

AB Two efficient routes for the total synthesis of (-)-epothilone B (I) are reported. One strategy is based on ring-closing metathesis, and a second synthesis on a macrolactonization. The key fragments are available on large scale to provide sufficient material for biol. tests. Thiazole fragment II (TBDMS = SiMe2CMe3) was obtained by an improved route starting from (S)-malic acid. The first synthesis is based on our preceding paper. The critical trisubstituted double bond C12-13 in our second approach was constructed by a highly efficient Pd-mediated coupling reaction. Ring closure was achieved by macrolactonization.

RX(79) OF 215 COMPOSED OF RX(12), RX(21), RX(10), RX(22)
RX(79) 2 AT + 2 ***AU*** + 2 AP + 2 V ===> ***BY*** + BZ

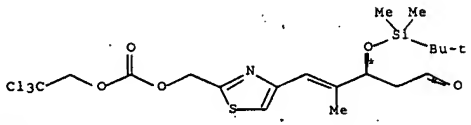
water solubility, and can serve as a readily functionalizable handle to produce other useful compds. for pertinent biol. studies.

RX(33) OF 128 COMPOSED OF RX(7), RX(1), RX(9), RX(10)
RX(33) 2 AG + 2 ***AH*** + 2 A + AS ===> ***AT*** + AU

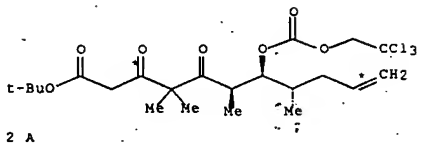


2 AG

AH



AH



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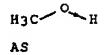
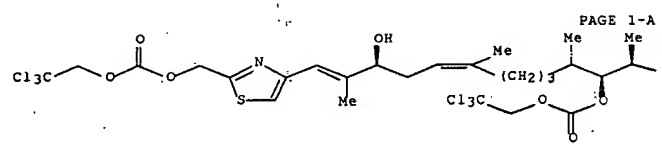


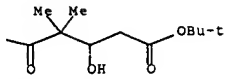
AS

4 STEPS



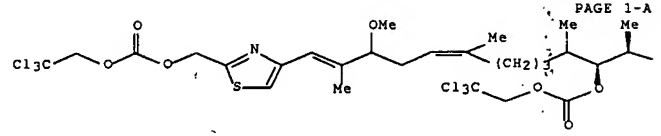
PAGE 1-A

PAGE 1-B



AT
YIELD 42%

PAGE 1-A



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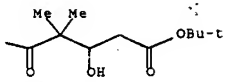

AU
YIELD 49%

RX(7) RCT AG 82294-38-0

STAGE(1)
RGT AI 109-72-8 BuLi
SOL 109-99-9 THF

STAGE(2)
RGT AJ 7553-56-2 I2
SOL 109-99-9 THF

STAGE(3)
RGT AK 1070-89-9 (Me3Si)2N.Na

STAGE(4)
RCT AH ***298702-12-2***
SOL 109-99-9 THF

```
            STAGE(4)
               RCT  EP 107905-52-2
               RGT  ES 17455-13-9 18-Crown-6, BJ 40949-94-8 K [N(SiMe3)2]
               SOL  109-99-9 THF

            STAGE(5)
               RGT  AK 12125-02-9 NH4Cl
               SOL  7732-18-5 Water, 60-29-7 Et2O

          PRO  EU 218614-04-1
          NTE  stereoselective

RX(61)    RCT  EU 218614-04-1

            STAGE(1)
               RGT  AN 1191-15-7 AlH(Bu-i)2
               SOL  109-99-9 THF, 142-82-5 Heptane

            STAGE(2)
               RGT  AO 304-59-6 Rochelle salt
               SOL  67-56-1 MeOH, 60-29-7 Et2O

          PRO  EX 218614-16-5

RX(55)    RCT  EX 218614-16-5

            STAGE(1)
               RGT  EF 603-35-0 PPh3
               SOL  75-05-8 MeCN, 60-29-7 Et2O

            STAGE(2)
               RGT  CB 288-32-4 1H-Imidazole

            STAGE(3)
               RGT  EY 7553-56-2 I2

            STAGE(4)
               RCT  ED 218613-98-0
               RGT  ES 17455-13-9 18-Crown-6, BJ 40949-94-8 K [N(SiMe3)2]
               SOL  109-99-9 THF

            STAGE(5)
               SOL  109-99-9 THF

            STAGE(6)
               RGT  AK 12125-02-9 NH4Cl
               SOL  7732-18-5 Water

          PRO  CV 308357-81-5
          NTE  diastereomeric mixt.

RX(28)    RCT  CV 308357-81-5
          RGT  CX 7558-79-4 Na2HPO4, CY 11110-52-4 Sodium amalgam
          PRO  CW 210690-85-0
          SOL  67-56-1 MeOH, 109-99-9 THF

RX(29)    RCT  CW 210690-85-0

            STAGE(1)
               RGT  DA 3144-16-9 10-CSA
```



```
               SOL  67-56-1 MeOH, 75-09-2 CH2Cl2

            STAGE(2)
               RGT  D 144-55-8 NaHCO3
               SOL  7732-18-5 Water

          PRO  CZ 210690-99-6

RX(56)    RCT  CZ 210690-99-6
          RGT  BT 77-76-9 Me2C(OMe)2
          PRO  FA 193146-27-9
          SOL  75-09-2 CH2Cl2, 110-86-1 Pyridine

RX(57)    RCT  CU 187527-25-9

            STAGE(1)
               RGT  W 4111-54-0 LiN(Pr-i)2
               SOL  109-99-9 THF

            STAGE(2)
               RCT  FA 193146-27-9
               SOL  109-99-9 THF

            STAGE(3)
               RGT  AK 12125-02-9 NH4Cl
               SOL  7732-18-5 Water

          PRO  FB 193146-50-8, DB 193146-49-5
REFERENCE COUNT:          41    THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT


L33  ANSWER 21 OF 23  CASREACT  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         133:266634  CASREACT  Full-text
TITLE:                    Total Synthesis and Antitumor Activity of
                          12,13-Desoxyepothilone F: An Unexpected Solvolysis
                          Problem at C15, Mediated by Remote Substitution at C21
AUTHOR(S):                Lee, Chul Bom; Chou, Ting-Chao; Zhang, Xiu-Guo; Wang,
                          Zhi-Guang; Kuduk, Scott D.; Chappell, Mark D.;
                          Stachel, Shawn J.; Danishefsky, Samuel J.
CORPORATE SOURCE:         Laboratory for Bioorganic Chemistry, The
                          Sloan-Kettering Institute for Cancer Research, New
                          York, NY, 10021, USA
SOURCE:                   Journal of Organic Chemistry (2000), 65(20), 6525-6533
                          CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER:                American Chemical Society
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   A new epothilone analog, 12,13-desoxyepothilone F (dEpoF, 21-hydroxy-12,13-
     desoxyepothilone B, 21-hydroxyepothilone D), was synthesized and evaluated for
     antitumor potential. A convergent strategy employed for the semi-practical
     synthesis of 12,13-desoxyepothilone B (dEpoB) has been utilized to yield an
     amount of dEpoF sufficient for relevant biol. studies. The results from an in
     vitro assay reveal that this new analog is highly active against various tumor
     cell lines with a potency comparable to that of dEpoB. In particular, the
     growth of resistant tumor cells is inhibited by dEpoF at concns. where
     paclitaxel (Taxol) is basically ineffective. A preliminary assessment of its
     in vivo activity is also promising. The new analog, containing an addnl.
     hydroxyl group at C21, exhibits advantages over other epothilones in terms of
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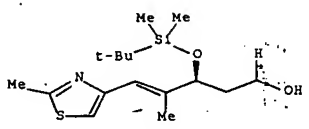
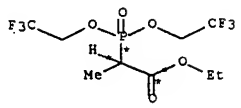


2 ET



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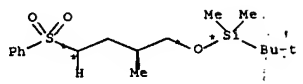

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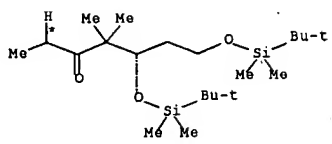
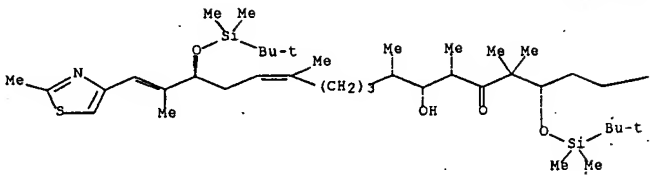


2 CU

7 STEPS

PAGE 1-A



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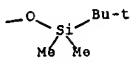
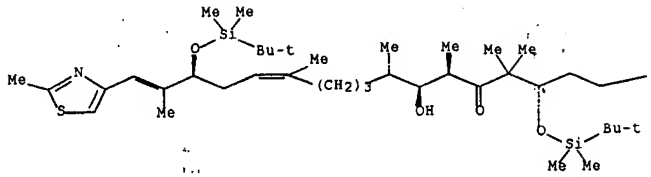


FB
YIELD 69%(80)

PAGE 1-A



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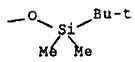


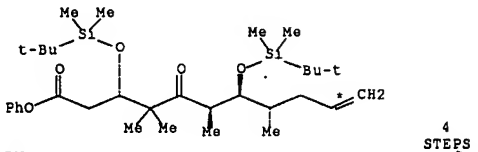
DB
YIELD 69%(80)

RX(52) RCT ET ***188899-14-1***

STAGE(1)
RGT R 79-37-8 (COCl)2, S 67-68-5 DMSO
SOL 75-09-2 CH2Cl2

STAGE(2)
RGT T 7087-68-5 EtN(Pr-i)2

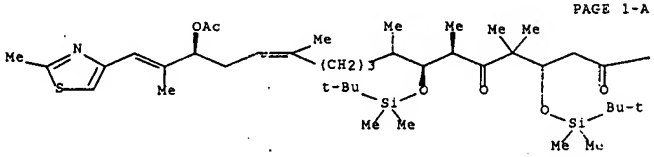
STAGE(3)
RGT AK 12125-02-9 NH4Cl
SOL 60-29-7 Et2O, 7732-18-5 Water



BV

4 STEPS

PAGE 1-A



PAGE 1-B

OPh

CJ
YIELD 50%

RX(15) RCT BG ***188730-08-7***, BH 4736-60-1

STAGE(1)
RGT BJ 109-72-8 BuLi
SOL 109-99-9 THF

STAGE(2)
RGT AZ 7553-56-2 I2

STAGE(3)
RGT BK 1070-89-9 (Me3Si)2N.Na

PRO BI 210690-66-7
NTE STEREOSELECTIVE

RX(16) RCT BI 210690-66-7
RGT BA 7664-39-3 HF, BB 110-86-1 Pyridine
PRO BL 312730-71-5
SOL 109-99-9 THF
NTE STEREOSELECTIVE

RX(17) RCT BL 312730-71-5, BC 108-24-7
RGT BE 121-44-8 Et3N, BF 1122-58-3 4-DMAP
PRO BM 189453-18-7
SOL 75-09-2 CH2Cl2
NTE STEREOSELECTIVE

RX(26) RCT BV 262375-53-1, BM 189453-18-7

STAGE(1)
RGT CM 280-64-8 9-BBN
SOL 109-99-9 THF

STAGE(2)
RGT CN 7778-53-2 K3PO4
CAT 72287-26-4 Palladium, [1,1'-bis(diphenylphosphino-κP)ferrocene]dichloro-, (SP-4-2)-
SOL 68-12-2 DMF, 7732-18-5 Water

PRO CJ ***312730-85-1***
NTE ULTRASOUND IN FIRST STAGE, STEREOSELECTIVE
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 20 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 134:4795 CASREACT Full-text
TITLE: Total Syntheses of Epothilones B and D
AUTHOR(S): Mulzer, Johann; Mantoulidis, Andreas; Oehler, Elisabeth
CORPORATE SOURCE: Institut fuer Organische Chemie, Universitaet Wien, Vienna, A-1090, Austria
SOURCE: Journal of Organic Chemistry (2000), 65(22), 7456-7467
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Total syntheses of the microtubule stabilizing antitumor drugs epothilone B and D are described, starting from optically pure (S)-malic acid and Me (R)-3-hydroxy-2-methylpropionate. The synthesis is highly convergent by coupling the three fragments C1-C6 (fragment D), C7-C10 (fragment C), and C11-C21 (fragment B). Key steps are two stereoselective Wittig type olefinations to generate the 12,13- and 16,17-double bonds, an enantioselective Mukaiyama aldol addition to synthesize fragment D, and a sulfone anion allyl iodide alkylation to connect fragments B and C. Finally fragment D was attached to the B + C fragment via aldol addition

RX(411) OF 711 COMPOSED OF RX(52), RX(61), RX(55), RX(28), RX(29), RX(56), RX(57)
RX(411) 2 ***ET*** + 2 EP + 2 ED + 2 CU ===> ***FB*** + DB

STAGE(1)
RGT AW 4111-54-0 LiN(Pr-i)2
SOL 109-99-9 THF

STAGE(2)
RCT AS 312492-69-6
SOL 109-99-9 THF

STAGE(3)
RGT J 12125-02-9 NH4Cl
SOL 7732-18-5 Water

PRO AV 321522-36-5

RX(13) RCT AV 321522-36-5, AX 17341-93-4

STAGE(1)
RGT T 110-86-1 Pyridine
SOL 75-09-2 CH2Cl2

STAGE(2)
RGT Y 144-55-8 NaHCO3
SOL 7732-18-5 Water

PRO AY 321522-37-6

RX(14) RCT AY 321522-37-6

STAGE(1)
RGT BA 20816-12-0 OsO4, BB 7529-22-8 Me-morpholineoxide
SOL 109-99-9 THF, 75-65-0 t-BuOH, 7732-18-5 Water

STAGE(2)
RGT V 7772-98-7 Na2S2O3
SOL 7732-18-5 Water, 75-09-2 CH2Cl2

STAGE(3)
RGT C 10028-15-6 Ozone
SOL 64-17-5 EtOH, 7732-18-5 Water

STAGE(4)
RGT Y 144-55-8 NaHCO3
SOL 7732-18-5 Water

PRO AZ ***321522-38-7***

L33 ANSWER 19 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 134:56502 CASREACT Full-text
TITLE: Enantioselective Total Synthesis of Epothilones A and B Using Multifunctional Asymmetric Catalysis
AUTHOR(S): Sawada, Daisuke; Kanai, Motomu; Shibasaki, Masakatsu
CORPORATE SOURCE: Graduate School of Pharmaceutical Sciences, The University of Tokyo, Bunkyo-ku Tokyo, 113-0033, Japan
SOURCE: Journal of the American Chemical Society (2000), 122(43), 10521-10532
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal

LANGUAGE: English
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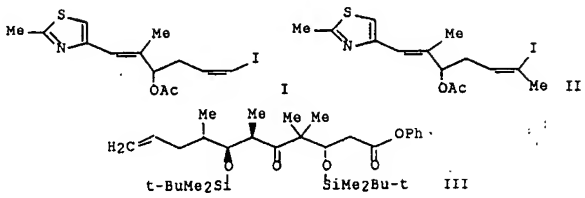
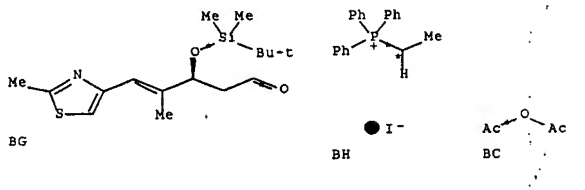
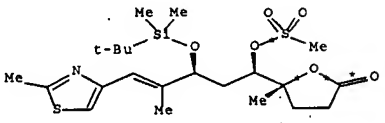


AB An enantioselective total synthesis of epothilones A and B using multifunctional asym. catalysis such as a cyanosilylation of an aldehyde, an aldol reaction of an unmodified ketone with an aldehyde, and a protonation in the conjugate addition of a thiol to an α,β-unsatd. thioester has been achieved. Epothilones A and B were divided into fragment A (I), fragment B (II), and fragment C (III). A catalytic asym. synthesis of fragments A and B was accomplished using a catalytic asym. cyanosilylation as a key step. An enantiocontrolled synthesis of fragment C was achieved in two ways. One is the use of a direct catalytic asym. aldol reaction of an unmodified ketone with an aldehyde as a key step, and the other utilizes a catalytic asym. protonation in the conjugate addition of a thiol to an α,β-unsatd. thioester as a key step. Suzuki cross-coupling of fragment A with fragment C followed by Yamaguchi lactonization as key steps led to an enantiocontrolled synthesis of epothilone A. On the other hand, Suzuki cross-coupling of fragment B with fragment C followed by Yamaguchi lactonization accomplished an enantiocontrolled synthesis of epothilone B.

RX(90) OF 319 COMPOSED OF RX(15), RX(16), RX(17), RX(26)
RX(90) ***BG*** + BH + BC + BV ===> ***CJ***





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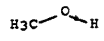
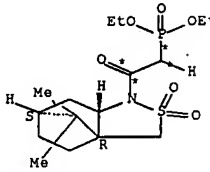
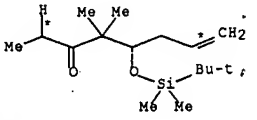


G

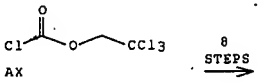


AJ

AN

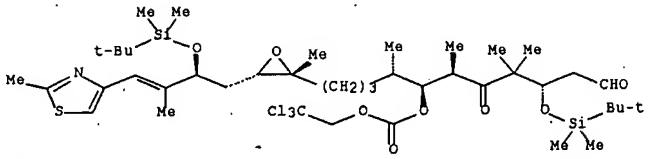


AU



AX

8 STEPS



AZ
YIELD 78%

RX(8) RCT AF *321522-34-3*, G 67-56-1
RGT AH 584-08-7 K2CO3
PRO AI 263761-11-1

SOL 67-56-1 MeOH
NTE stereoselective

RX(19) RCT AI 263761-11-1

STAGE(1)
RGT AT 1191-15-7 AlH(Bu-i)2
SOL 75-09-2 CH2Cl2

STAGE(2)
RGT J 12125-02-9 NH4Cl
SOL 7732-18-5 Water

PRO AK 263761-13-3

RX(9) RCT AJ 263768-73-6

STAGE(1)
RGT AM 109-72-8 BuLi
SOL 60-29-7 Et2O, 109-99-9 THF, 7732-18-5 Water

STAGE(2)
RCT AK 263761-13-3
SOL 109-99-9 THF

STAGE(3)
RGT J 12125-02-9 NH4Cl
SOL 7732-18-5 Water

PRO AL 263761-14-4

RX(10) RCT AL 263761-14-4

STAGE(1)
RGT AQ 38721-52-7 L-Selectride
SOL 109-99-9 THF

STAGE(2)
RCT AN 74-88-4
RGT AR 680-31-9 HMPT

STAGE(3)
RGT J 12125-02-9 NH4Cl
SOL 7732-18-5 Water

PRO AO 263761-15-5, AP 321522-35-4

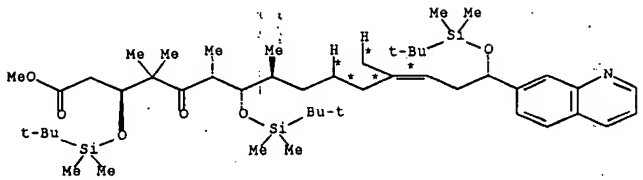
RX(11) RCT AO 263761-15-5

STAGE(1)
RGT AT 1191-15-7 AlH(Bu-i)2
SOL 75-09-2 CH2Cl2

STAGE(2)
RGT J 12125-02-9 NH4Cl
SOL 67-56-1 MeOH, 7732-18-5 Water, 60-29-7 Et2O

PRO AS 312492-69-6

RX(12) RCT AU 187283-44-9



L
YIELD 90%

RX(9) RCT AP 271792-03-1

STAGE(1)
RGT AQ 1070-89-9 (Me3Si)2N.Na
SOL 109-99-9 THF

STAGE(2)
RCT AN ***279226-92-5***

PRO K 279226-93-6
NTE stereoselective

RX(2) RCT J 279227-12-2

STAGE(1)
RGT M 280-64-8 9-BBN
SOL 109-99-9 THF

STAGE(2)
RCT K 279226-93-6
RGT N 534-17-8 Cs2CO3, O 603-32-7 Ph3As
CAT 51364-51-3 Ph2-pentadienone Pd
SOL 68-12-2 DMF

PRO L ***279226-94-7***
NTE stereoselective

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 18 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 134:115799 CASREACT Full-text
TITLE: Process for the production of epothilone B and derivatives as well as intermediate products for this process
INVENTOR(S): Mulzer, Johann; Martin, Harry
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 50 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007439	A2	20010201	WO 2000-US20064	20000724
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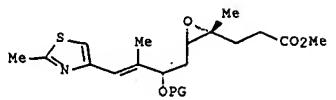
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1226142	A2	20020731	EP 2000-948907	20000724
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003505459	T	20030212	JP 2001-512523	20000724
NO 2002000308	A	20020321	NO 2002-308	20020121
PRIORITY APPLN. INFO.:			US 1999-145005P	19990722
			WO 2000-US20064	20000724

OTHER SOURCE(S): MARPAT 134:115799
GI



I

AB The present invention is directed to a process for the production of epothilone B compds., the improvement comprising preparing said compds. by cyclization of a compound produced from an intermediate of formula (I) wherein PG is a protecting group.

RX(107) OF 190 COMPOSED OF RX(8), RX(19), RX(9), RX(10), RX(11), RX(12), RX(13), RX(14)
RX(107) ***AF*** + G + AJ + AN + AU + AX ===> ***AZ***

RGT CD 7553-56-2 I2

PRO CB 335160-07-1
NTE stereoselective

RX(32) RCT CB 335160-07-1, BM 113453-27-3
RGT CF 7440-66-6 Zn, CG 7440-50-8 Cu
PRO CE 335160-08-2
CAT 14221-01-3 Pd(PPh3)4
SOL 71-43-2 Benzene
NTE stereoselective

RX(33) RCT CE 335160-08-2
RGT AF 3144-16-9 10-CSA
PRO CI 335160-09-3
SOL 67-56-1 MeOH
NTE stereoselective

RX(34) RCT CI 335160-09-3
RGT F 79-37-8 (COCl)2, Z 67-68-5 DMSO
PRO CJ 335160-10-6
SOL 75-09-2 CH2Cl2
NTE stereoselective

RX(35) RCT CJ 335160-10-6, AL 187283-45-0

STAGE(1)

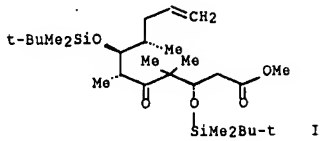
STAGE(2)
RCT AM 69739-34-0
RGT AP 108-48-5 2,6-Lutidine

STAGE(3)
RGT AQ 584-08-7 K2CO3
SOL 67-56-1 MeOH

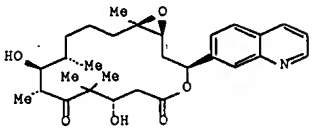
PRO CK ***335160-11-7***
NTE stereoselective

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 17 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 134:178371 CASREACT Full-text
TITLE: Synthesis and biological evaluation of highly potent analogues of epothilones B and D
AUTHOR(S): Altmann, K.-H.; Bold, G.; Caravatti, G.; Florsheimer, A.; Guagnano, V.; Wartmann, M.
CORPORATE SOURCE: Novartis Pharma AG, TA Oncology Research, Basel, CH-4002, Switz.
SOURCE: Bioorganic & Medicinal Chemistry Letters (2000), 10(24), 2765-2768
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



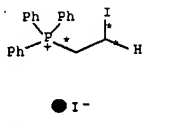
I



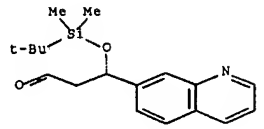
II

AB A series of new epothilone B and D analogs incorporating fused hetero-aromatic side chains have been prepared The synthetic strategy is based on olefin I as the common intermediate and allows variation of the side-chain structure in a highly convergent and stereoselective manner. These epothilone analogs, e.g. II, are more potent inhibitors of cancer cell proliferation than the corresponding parent epothilones B or D.

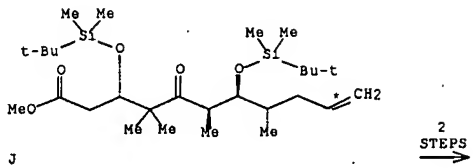
RX(27) OF 370 COMPOSED OF RX(9), RX(2)
RX(27) AP + ***AN*** + J ===> ***L***



AP

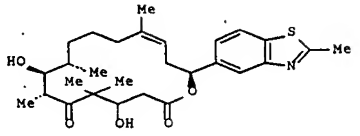


AN



J

Wartmann, Markus; Altmann, Karl-Heinz
CORPORATE SOURCE: TA Oncology Research, Novartis Pharma AG, Basel, CH-4002, Switz.
SOURCE: Proceedings of ECSOC-3, [and] Proceedings of ECSOC-4, Sept. 1-30, 1999 and 2000 (2000), Meeting Date 1999-2000, 1431-1442. Editor(s): Pombo-Villar, Esteban. Molecular Diversity Preservation International: Basel, Switz.
CODEN: 69AXZT
DOCUMENT TYPE: Conference; (computer optical disk)
LANGUAGE: English
GI

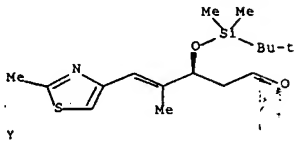


I

AB The authors have synthesized epothilone analogs, e.g. I, with modifications in the northern hemisphere and the heterocyclic side-chain. In all three cases the key steps for construction of the macrocyclic skeleton involve Yamaguchi macrolactonization, the build-up of the requisite seco-acid through aldol reaction between the C7-C15 aldehyde and the dianion of the O-protected C1-C6 β-hydroxy acid fragment, and the assembly of the C7-C15 aldehyde through the appropriate type of Pd(0)-catalyzed coupling reaction. The IC50 for growth inhibition of the KB-31 tumor cell line for I was 0.45 nM.

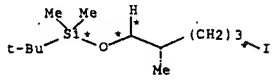
RX(284) OF 370 COMPOSED OF RX(29), RX(30), RX(31), RX(32), RX(33), RX(34), RX(35)

RX(284) **Y** + BX + BM + AL + AM ===> **CK**

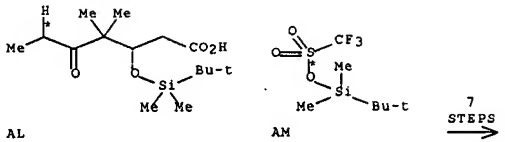


Y

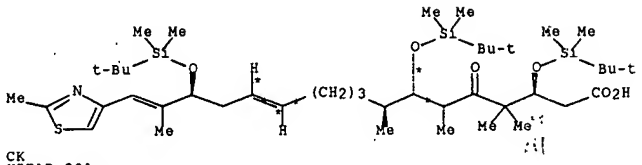
BX



BM



AL AM



CK
YIELD 30%

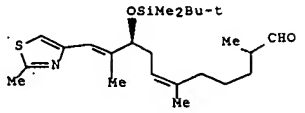
RX(29) RCT Y **188730-08-7**, BX 558-13-4
RGT BZ 603-35-0 PPh3
PRO BY 335160-05-9
SOL 75-09-2 CH2Cl2
NTE stereoselective

RX(30) RCT BY 335160-05-9
RGT K 109-72-8 BuLi
PRO CA 335160-06-0
SOL 109-99-9 THF
NTE stereoselective

RX(31) RCT CA 335160-06-0

STAGE(1)
RGT CC 1291-32-3 ZrCp2Cl2
SOL 109-99-9 THF

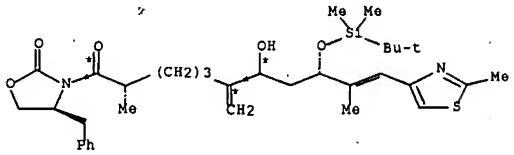
STAGE(2)



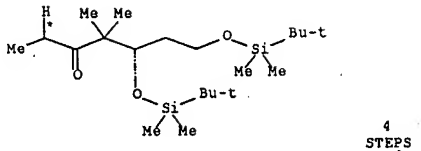
I

AB A highly convergent total synthesis of the natural products epothilone B and D is described. The route is highlighted by efficient generation of a C12-C13 trisubstituted olefin I which exploits a sequential Nozaki-Hiyama-Kishi coupling and a stereoselective thionyl chloride rearrangement.

RX(53) OF 175 COMPOSED OF RX(6), RX(7), RX(13), RX(14)
RX(53) O + N ===> AN



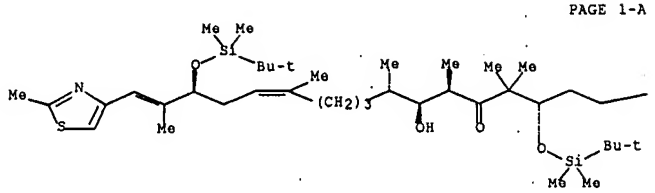
O



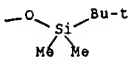
N

4 STEPS

PAGE 1-A



PAGE 1-B



AN
YIELD 83%

RX(6) RCT O ***355009-06-2***
RGT U 7719-09-7 SOCl2
PRO T 355009-08-4
SOL 60-29-7 Et2O, 109-66-0 Pentane

RX(7) RCT T 355009-08-4
RGT Y 22560-16-3 Superhydride
PRO X 210690-99-6
SOL 109-99-9 THF
NTE other product detected

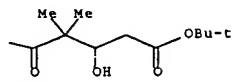
RX(13) RCT X 210690-99-6
RGT AC 26299-14-9 PCC
PRO AM 193146-27-9

RX(14) RCT N 187527-25-9, AM 193146-27-9
RGT AO 4111-54-0 LiN(Pr-i)2
PRO AN ***193146-49-5***
NTE stereoselective, other product detected, no exptl.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 16 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 134:311010 CASREACT Full-text
TITLE: Synthetic epothilone analogs with modifications in the northern hemisphere and the heterocyclic side-chain-synthesis and biological evaluation
AUTHOR(S): End, Nicole; Bold, Guido; Caravatti, Giorgio;

PAGE 1-B



AU
YIELD 42%

RX(6) RCT Z 4736-60-1

STAGE(1)
RGT AC 109-72-8 BuLi
SOL 109-99-9 THF

STAGE(2)
RGT AD 7553-56-2 I2
SOL 109-99-9 THF

STAGE(3)
RGT AE 1070-89-9 (Me3Si)2N.Na

STAGE(4)
RCT AA ***298702-12-2***
SOL 109-99-9 THF

STAGE(5)
RGT D 64-19-7 AcOH

PRO AB 298702-07-5
NTE STEREOSELECTIVE

RX(8) RCT AL 224580-52-3

STAGE(1)
RGT AN 280-64-8 9-BBN
SOL 109-99-9 THF

STAGE(2)
RCT AB 298702-07-5
RGT AO 603-32-7 Ph3As, AP 534-17-8 Cs2CO3
CAT 72287-26-4 Palladium, [1,1'-bis(diphenylphosphino-κP)ferrocene]dichloro-, (SP-4-2)-
SOL 68-12-2 DMF

STAGE(3)
SOL 7732-18-5 Water

STAGE(4)
SOL 60-29-7 Et2O

PRO AM 298702-16-6

NTE STEREOSELECTIVE

RX(9) RCT AM 298702-16-6

STAGE(1)
RGT AS 7647-01-0 HCl
SOL 67-56-1 MeOH

STAGE(2)
RGT N 144-55-8 NaHCO3

STAGE(3)
SOL 75-09-2 CH2Cl2

PRO AR 298702-17-7
NTE STEREOSELECTIVE

RX(10) RCT AR 298702-17-7, AT 67-56-1

STAGE(1)
RGT AS 7647-01-0 HCl
CAT 109361-17-3 Ruthenium, bis[(1R)-[1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine-κP]]di-μ-chlorodichloro(N,N-diethylethanamine)di-
SOL 67-56-1 MeOH

STAGE(2)
RGT AV 1333-74-0 H2

STAGE(3)
RGT N 144-55-8 NaHCO3

STAGE(4)
SOL 75-09-2 CH2Cl2

PRO AU ***298702-19-9***
NTE STEREOSELECTIVE

L33 ANSWER 15 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 135:180642 CASREACT Full-text
TITLE: Total Synthesis of Epothilones B and D
AUTHOR(S): Taylor, Richard E.; Chen, Yue
CORPORATE SOURCE: Department of Chemistry & Biochemistry, University of Notre Dame, Notre Dame, IN, 46556-5670, USA
SOURCE: Organic Letters (2001), 3(14), 2221-2224
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI

ACCESSION NUMBER: 135:226826 CASREACT Full-text
TITLE: Synthesis of epothilones, intermediates and analogs for use in treatment of cancers with multidrug resistant phenotype
INVENTOR(S): Danishefsky, Samuel J.; Lee, Chul Bom; Chappell, Mark; Stachel, Shawn; Chou, Ting-chao
PATENT ASSIGNEE(S): Sloan-Kettering Institute for Cancer Research, USA
SOURCE: PCT Int. Appl., 234 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001064650	A2	20010907	WO 2001-US6643	20010301
WO 2001064650	A3	20020510		
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2401800	A1	20010907	CA 2001-2401800	20010301
EP 1259490	A2	20021127	EP 2001-916335	20010301
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004500388	T	20040108	JP 2001-563492	20010301
PRIORITY APPLN. INFO.:			US 2000-185968P	20000301
			US 2000-250447P	20001130
			WO 2001-US6643	20010301

OTHER SOURCE(S): MARPAT 135:226826
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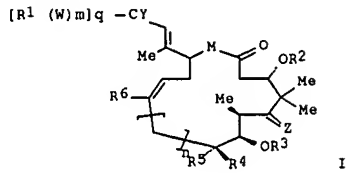
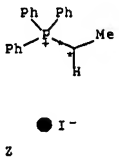


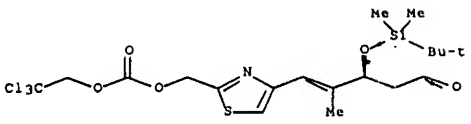
I

AB The present invention provides convergent processes for preparing epothilones, desoxyepothilones, and analogs, e.g., I [M = NH, O; CY = aryl, heteroaryl; q = 1-5; W = absent, NH, CO, CS, O, S, C(V)2; V = H, halogen, OH, SH, amino, (un)substituted alkyl, heteroalkyl, aryl, heteroaryl; m = 1-5; bond W···R1 = single bond, double bond; R1 = OR, SR, NR2; CO2R, COR, CONHR, N3, N2, N2R; halogen, un(substituted) cyclic or acyclic aliphatic, heteroaliph., aryl or heteroaryl, polymer, carbohydrate; R = H, un(substituted) cyclic or acyclic aliphatic, heteroaliph., aryl or heteroaryl, protecting group; R2, R3 = H, un(substituted) aliphatic, heteroaliph., aryl, heteroaryl, acyl, aroyl, benzoyl; R4, R5 = H, un(substituted) cyclic or acyclic aliphatic, heteroaliph., aryl or heteroaryl, optionally substituted by one or more of OH, alkoxy, carboxy, carboxaldehyde, N-alkoxyimino, N-alkoxyimino; R6 = H, OR, SR, NR2; CO2R, COR, CONHR, N3, N2, N2R, cyclic acetal, halogen, un(substituted) cyclic or acyclic aliphatic, aryl, heteroaryl; Z = O, N(ORE), NNRFRG; RE, RF, RG = un(substituted) cyclic or acyclic aliphatic; n = 0-3], for the treatment of cancer. Biol. activities of novel compds. based on I and methods for the treatment of cancer and cancer which has developed a multi-drug phenotype are presented. Thus, 21-oxo-12,13-desoxyepothilone B and 15-azaepothilone B were active vs leukemia CCRF-CEM cells (IC50 = 0.027 μM; IC50 = 0.021 μM, resp.).

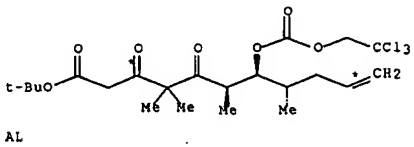
RX(112) OF 295 COMPOSED OF RX(6), RX(8), RX(9), RX(10)
RX(112) Z + **AA** + AL + AT ===> ***AU***



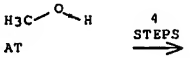
Z



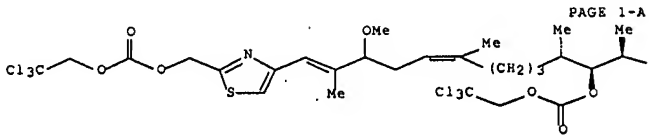
AA



AL



AT



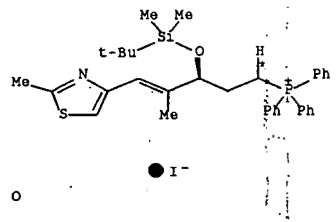
ACCESSION NUMBER: 135:287591 CASREACT Full-text
TITLE: Preparation of epothilone intermediates
INVENTOR(S): Vite, Gregory D.; Kim, Soong-Hoon; Hoeefle, Gerhard
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

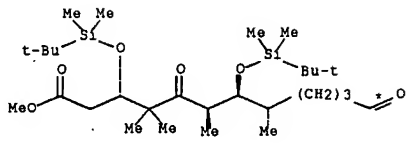
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001073103	A2	20011004	WO 2001-US9620	20010323
WO 2001073103	A3	20020523		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002042109	A1	20020411	US 2001-811808	20010319
US 6593115	B2	20030715		
US 2004023345	A1	20040205	US 2003-447082	20030528
PRIORITY APPLN. INFO.:			US 2000-191975P	20000324
			US 2001-811808	20010319

OTHER SOURCE(S): MARPAT 135:287591

AB The present invention relates to a process for the preparation of intermediates useful in the synthesis of epothilone analogs by initially enzymically degrading certain epothilone compds. to form ring-open structures containing a carboxyl group which is esterified, the hydroxyl groups on the moiety protected and the resulting compound oxidized by, e.g. ozone, to form a first intermediate. The first intermediate can be reacted with a triphenylphosphine adduct to yield a compound containing an ester group at position 1 which is subsequently hydrolyzed to form a second intermediate.

RX(4) OF 31 ...O + P ===> Q...

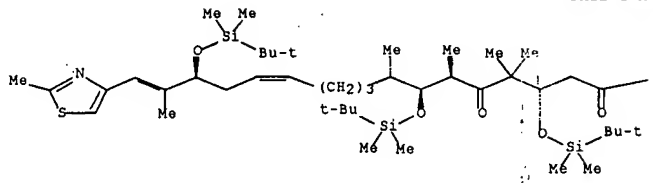




P

(4)

PAGE 1-A



PAGE 1-B

OMe

Q

YIELD 55%

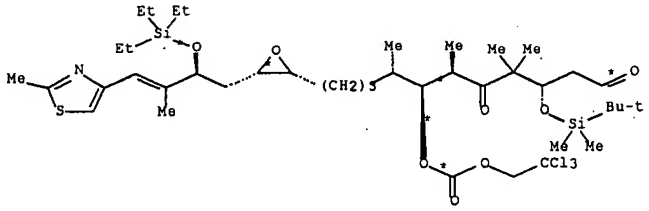
RX(4) RCT O *190369-98-3*

STAGE(1)
RGT R 1070-89-9 (Me3Si)2N.Na
SOL 109-99-9 THF

STAGE(2)
RCT P 364336-83-4
SOL 109-99-9 THF

PRO Q *364336-77-6*

L33 ANSWER 14 OF 23 CASREACT COPYRIGHT 2007 ACS on STN



EP
YIELD 86%

RX(6) RCT AB ***370578-43-1***

STAGE(1)
RGT AD 121-44-8 Et3N
SOL 75-09-2 CH2Cl2

STAGE(2)
RGT AE 7719-09-7 SOCl2
SOL 75-09-2 CH2Cl2

STAGE(3)
RGT G 7732-18-5 Water

STAGE(4)
RGT AF 429-41-4 Bu4N.F
SOL 109-99-9 THF

PRO AC 370578-22-6
NTE stereoselective

RX(64) RCT AC 370578-22-6, EM 994-30-9

STAGE(1)
RGT AD 121-44-8 Et3N
CAT 1122-58-3 4-DMAP
SOL 75-09-2 CH2Cl2

STAGE(2)
RGT D 144-55-8 NaHCO3
SOL 7732-18-5 Water

PRO DL 370578-62-4

RX(32) RCT DL 370578-62-4

STAGE(1)

RGT CK 7529-22-8 Me-morpholineoxide
SOL 75-65-0 t-BuOH, 109-99-9 THF, 7732-18-5 Water

STAGE(2)
CAT 20816-12-0 OsO4
SOL 7732-18-5 Water

STAGE(3)
RGT DN 7631-90-5 NaHSO3

STAGE(4)
RGT DO 546-67-8 Pb(OAc)4
SOL 141-78-6 AcOEt

PRO DM 342607-03-8

RX(33) RCT DQ 219990-08-6

STAGE(1)
RGT AU 4111-54-0 LiN(Pr-i)2
SOL 109-99-9 THF

STAGE(2)
RCT DM 342607-03-8
SOL 109-99-9 THF

STAGE(3)
RGT AA 12125-02-9 NH4Cl
SOL 7732-18-5 Water

PRO DR 342607-02-7
NTE in-situ generated reagent, stereoselective

RX(66) RCT DR 342607-02-7, FO 17341-93-4
RGT E 110-86-1 Pyridine
PRO EO 342607-17-4
SOL 75-09-2 CH2Cl2

RX(45) RCT EO 342607-17-4

STAGE(1)
RGT CK 7529-22-8 Me-morpholineoxide
SOL 75-65-0 t-BuOH, 109-99-9 THF, 7732-18-5 Water

STAGE(2)
CAT 20816-12-0 OsO4

STAGE(3)
RGT DN 7631-90-5 NaHSO3

STAGE(4)
RGT DO 546-67-8 Pb(OAc)4
SOL 141-78-6 AcOEt

PRO EP ***342607-35-6***
REFERENCE COUNT: 99 THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 13 OF 23 CASREACT COPYRIGHT 2007 ACS on STN

STAGE(2)
RGT Z 109-72-8 BuLi
SOL 109-99-9 THF

STAGE(3)
RGT CJ 37342-97-5 Hydrozirconocene Cl
SOL 109-99-9 THF

STAGE(4)
RGT CK 7553-56-2 I2
SOL 109-99-9 THF

PRO CH 335160-07-1

RX(30) RCT AO 113453-27-3, CH 335160-07-1

STAGE(1)
RGT CM 12621-78-2 Zinc alloy, base, Zn,Cu
CAT 14221-01-3 Pd(PPh3)4
SOL 71-43-2 Benzene

STAGE(2)
RGT BY 3144-16-9 10-CSA
SOL 67-56-1 MeOH

STAGE(3)
RGT BL 67-68-5 DMSO, AB 79-37-8 (COCl)2
SOL 75-09-2 CH2Cl2

PRO CL 335160-10-6

RX(31) RCT H 187283-45-0, CL 335160-10-6

STAGE(1)
RGT BT 4111-54-0 LiN(Pr-i)2

STAGE(2)
RCT F 69739-34-0
RGT BW 108-48-5 2,6-Lutidine

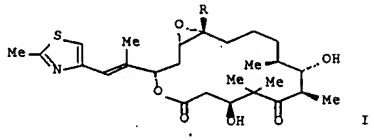
STAGE(3)
RGT CQ 584-08-7 K2CO3
SOL 67-56-1 MeOH

PRO CP 335160-11-7

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 12 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 135:331283 CASREACT Full-text
TITLE: Stereoselective Syntheses of Epothilones A and B via Nitrile Oxide Cycloadditions and Related Studies
AUTHOR(S): Bode, Jeffrey W.; Carreira, Erick M.
CORPORATE SOURCE: Laboratorium fuer Organische Chemie, ETH-Zuerich, Zurich, CH-8092, Switz.
SOURCE: Journal of Organic Chemistry (2001), 66(19), 6410-6424 CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal

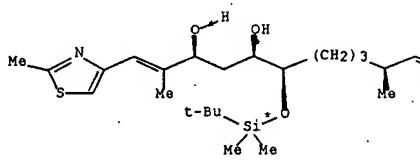
LANGUAGE: English
GI



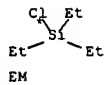
I

AB The expedient and fully stereocontrolled synthesis of epothilones A (I; R = H) and B I (R = Me) are described. The routes described make extensive study of nitrile oxide cycloaddns. as surrogates for aldol addition reactions and have led to the realization of a highly convergent synthesis based on the Kanemasa hydroxyl-directed nitrile oxide cycloaddn. As well, our synthetic efforts have led to the development of new reaction methodologies and served as the proving ground for several modern methods for asym. carbon-carbon bond formation.

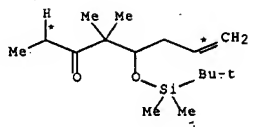
RX(451) OF 751 COMPOSED OF RX(6), RX(64), RX(32), RX(33), RX(66), RX(45)
RX(451) ***AB*** + EM + DQ + FO ===> ***EP***



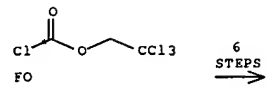
AB



EM



DQ



FO

6 STEPS

SOL 109-99-9 THF

PRO BR 186692-68-2
NTE stereoselective

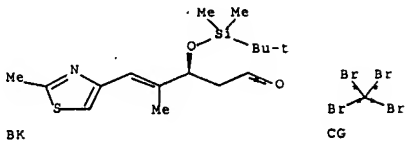
RX(28) RCT AX 461044-35-9, BR 186692-68-2
RGT BW 603-32-7 Ph3As, BX 534-17-8 Cs2CO3, BY 280-64-8 9-BBN
PRO BV ***461044-42-8***
CAT 72287-26-4 Palladium, [1,1'-bis(diphenylphosphino-κP)ferrocene]dichloro-, (SP-4-2)-
NTE stereoselective, regioselective

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

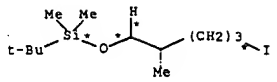
L33 ANSWER 11 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 136:318824 CASREACT Full-text
TITLE: Synthetic and semisynthetic analogs of epothilones: chemistry and biological activity
AUTHOR(S): Altmann, Karl-Heinz; Blommers, Marcel J. J.; Caravatti, Giorgio; Florsheimer, Andreas; Nicolaou, Kyriacos C.; O'Reilly, Terrence; Schmidt, Alfred; Schinzer, Dieter; Wartmann, Markus
CORPORATE SOURCE: TA Oncology Research, Novartis Pharma AG, Basel, CH-4002, Switz.
SOURCE: ACS Symposium Series (2001), 796(Anticancer Agents), 112-130
CODEN: ACSMC8; ISSN: 0097-6156
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Epothilones A and B are naturally occurring microtubule depolymn. inhibitors, which exhibit potent in vitro antiproliferative activity. Epothilone B is a 3-30-fold more potent inhibitor of human cancer cell growth than paclitaxel in paclitaxel-sensitive cancer cell lines and in paclitaxel-resistant lines exceeds paclitaxel activity by 102 - 103-fold. In addition, epothilone B exhibits potent in vivo antitumor activity even in multidrug-resistant tumor models. In order to gain a better understanding of the structural requirements for epothilone-mediated cytotoxicity and antitumor activity and to discover analogs with similar potency but perhaps better tolerability in vivo, we have investigated a series of structural modifications involving the epoxide site (C12/C13) and the heterocyclic side-chain of epothilones. In this paper we present the synthesis of these analogs and we discuss the impact of such modifications on tubulin polymerization activity as well as cytotoxicity in vitro.

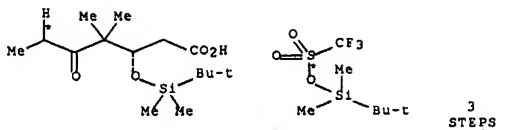
RX(146) OF 320 COMPOSED OF RX(29), RX(30), RX(31)
RX(146) ***BK*** + CG + AO + H + F ===> ***CP***



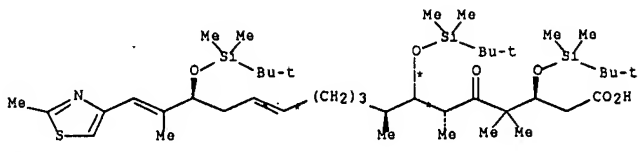
BK CG



AO



H F



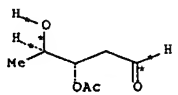
CP

RX(29) RCT BK ***188730-08-7***, CG 558-13-4

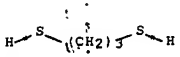
STAGE(1)
RGT CI 603-35-0 PPh3
SOL 75-09-2 CH2Cl2

of novel pyranose synthons. The utility of this very convergent and effective method is demonstrated by the concise total synthesis of epothilones. The stereoselective I-catalyzed aldol condensation of acetaldehyde with (2S)-3-hydroxy-2-methylpropanal gave 2,4-dideoxy-4-methyl-L-erythro-pentopyranose. Oxidation of the latter gave 2,4-dideoxy-4-methyl-L-threo-pentonic acid δ-lactone. Alkylation of the δ-lactone gave 2,4-dideoxy-4-methyl-2-(2-propenyl)-L-xylonic acid δ-lactone. This compound was a chiral synthon needed for the total synthesis of epothilone C [(4S,7R,8S,9S,13Z,16S)-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]oxacyclohexadec-13-ene-2,6-dione].

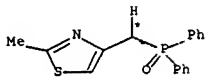
RX(172) OF 316 COMPOSED OF RX(23), RX(24), RX(25), RX(26), RX(27), RX(28)
RX(172) ***BC*** + BH + BN + BQ + AX ===> ***BV***



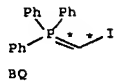
BC



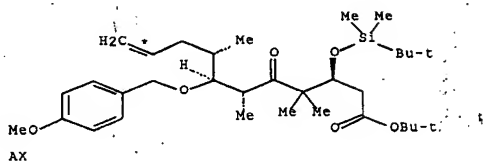
BH



BN

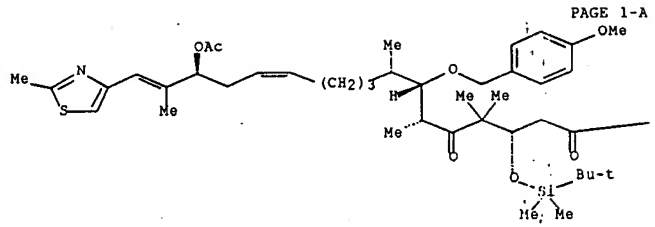


BQ



AX

6 STEPS →



PAGE 1-B

OBu-t

BV
YIELD 65%

RX(23) RCT BC ***247900-97-6***
RGT BF 109-63-7 BF3-Et2O
PRO BE 461044-38-2
SOL 7732-18-5 Water, 75-05-8 MeCN

RX(24) RCT BE 461044-38-2, BH 109-80-8
PRO BI 461044-39-3
CAT 7550-45-0 TiCl4

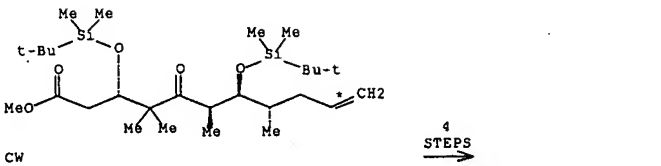
RX(25) RCT BI 461044-39-3
RGT BL 79-37-8 (COCl)2, BM 67-68-5 DMSO
PRO BK 461044-40-6

RX(26) RCT BK 461044-40-6, BN 184246-51-3
RGT AR 109-72-8 BuLi
PRO BO 461044-41-7
SOL 109-99-9 THF
NTE stereoselective

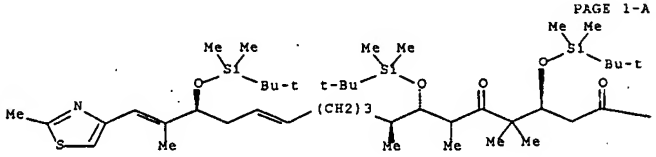
RX(27) RCT BO 461044-41-7

STAGE(1)
RGT BS 7616-83-3 Hg(ClO4)2, BT 471-34-1 CaCO3
SOL 109-99-9 THF, 7732-18-5 Water

STAGE(2)
RCT BQ 29949-93-7
RGT V 680-31-9 HMPT, BU 1070-89-9 (Me3Si)2N.Na



PAGE 1-A



PAGE 1-B

—OMe

BU
YIELD 63%

RX(18) RCT BF ***188730-08-7***, BH 558-13-4
RGT BJ 603-35-0 PPh3
PRO BI 335160-05-9
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) 10 minutes, 18 - 23 deg C
SUBSTAGE(2) 1 hour, room temperature

RX(19) RCT BI 335160-05-9
RGT AJ 109-72-8 BuLi
PRO L 335160-06-0
SOL 109-99-9 THF, 110-54-3 Hexane

CON SUBSTAGE(1) room temperature -> -75 deg C
SUBSTAGE(2) 30 minutes
SUBSTAGE(3) 1 hour, -75 deg C
SUBSTAGE(4) 1 hour, room temperature

RX(3) RCT L 335160-06-0

STAGE(1)
RGT N 37342-97-5 Hydrozirconocene Cl
SOL 109-99-9 THF
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 30 minutes, room temperature

STAGE(2)
RGT O 7553-56-2 I2
CON SUBSTAGE(1) 10 minutes, 20 - 25 deg C
SUBSTAGE(2) 10 minutes

PRO M 335160-07-1
NTE stereoselective

RX(39) RCT CW 279227-12-2

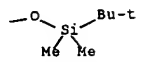
STAGE(1)
RGT DB 280-64-8 9-BBN
SOL 109-99-9 THF
CON 4 hours, room temperature

STAGE(2)
RCT M 335160-07-1
RGT DC 603-32-7 Ph3As, DD 534-17-8 Cs2CO3
CAT 72287-26-4 Palladium, [1,1'-bis(diphenylphosphino-κP)ferrocene]dichloro-, (SP-4-2)-
SOL 7732-18-5 Water, 68-12-2 DMF
CON SUBSTAGE(1) room temperature -> -10 deg C
SUBSTAGE(2) -10 deg C -> room temperature
SUBSTAGE(3) 24 hours, room temperature

PRO BU ***501691-10-7***
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 10 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 137:247231 CASREACT Full-text
TITLE: Aldolase-catalyzed asymmetric synthesis of novel pyranose synthons as a new entry to heterocycles and epothilones
AUTHOR(S): Liu, Junjie; Wong, Chi-Huey
CORPORATE SOURCE: Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Angewandte Chemie, International Edition (2002), 41(8), 1404-1407
CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Enzymic reactions catalyzed by DERA (2-deoxyribose-5-phosphate aldolase, deoxyriboaldolase, (I)) provide the basis for a new strategy for the synthesis

PAGE 1-B



BQ
YIELD 93%

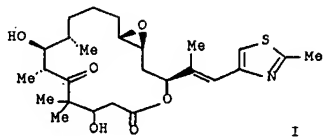
RX(27) RCT T ***193146-30-4D***

STAGE(1)
RGT BY 1070-89-9 (Me3Si)2N.Na
SOL 109-99-9 THF
CON 15 minutes, room temperature

STAGE(2)
RCT BP 346652-91-3
CON 15 minutes, -78 deg C -> -40 deg C

PRO BQ ***583829-96-3***
NTE solid-supported reaction
REFERENCE COUNT: 73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 9 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 138:237914 CASREACT Full-text
TITLE: The total synthesis and biological assessment of trans-epothilone A
AUTHOR(S): Altmann, Karl-Heinz; Bold, Guido; Caravatti, Giorgio; Denni, Donatienne; Florsheimer, Andreas; Schmidt, Alfred; Rihs, Grety; Wartmann, Markus
CORPORATE SOURCE: Corporate Research, Novartis Pharma AG, Switz.
SOURCE: Helvetica Chimica Acta (2002), 85(11), 4086-4110
CODEN: HCACAV; ISSN: 0018-019X
PUBLISHER: Verlag Helvetica Chimica Acta
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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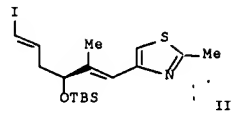

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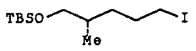
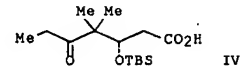


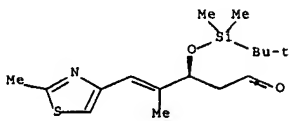
III



IV

AB The total synthesis of (12S,13S)-trans-epothilone A (I) was achieved based on two different convergent strategies. In a first-generation approach, construction of the C(11)-C(12) bond by Pd0-catalyzed Negishi-type coupling between the C(12)-to-C(15) trans-vinyl iodide II and the C(7)-to-C(11) alkyl iodide III preceded the (nonselective) formation of the C(6)-C(7) bond by aldol reaction between the C(7)-to-C(15) aldehyde and the dianion derived from the C(1)-to-C(6) acid IV. The lack of selectivity in the aldol step was addressed in a second-generation approach, which involved construction of the C(6)-C(7) bond in a highly diastereoselective fashion through reaction between the acetonide-protected C(1)-to-C(6) diol ("Schinzer's ketone") and the C(7)-to-C(11) aldehyde. As part of this strategy, the C(11)-C(12) bond was established subsequent to the critical aldol step and was based on B-alkyl Suzuki coupling between the C(1)-to-C(11) fragment and C(12)-to-C(15) trans-vinyl iodide II. Both approaches converged at the stage of the 3-O, 7-O-bis-TBS-protected seco acid, which was converted to trans-deoxyepothilone A via Yamaguchi macrolactonization and subsequent deprotection. Stereoselective epoxidn. of the trans C(12)-C(13) bond could be achieved by epoxidn. with Oxone in the presence of the catalyst 1,2:4,5-di-O-isopropylidene-L-erythro-2,3-hexodiuro-2,6-pyranose, which provided a 8:1 mixture of I and its (12R,13R)-epoxide isomer (V) in 27% yield (54% based on recovered starting material). The absolute configuration of I was established by X-ray crystallog. I is at least equipotent with natural epothilone A (VI) in its ability to induce tubulin polymerization and to inhibit the growth of human cancer cell lines in vitro. In contrast, the biol. activity of V is at least two orders of magnitude lower than that of VI or I.

RX(123) OF 496 COMPOSED OF RX(18), RX(19), RX(3), RX(39)
RX(123) ***BF*** + BH + CW ===> ***BU***



BF

BH

RGT CF 280-64-8 9-BBN
SOL 109-99-9 THF
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 3 hours, room temperature

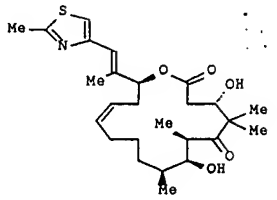
STAGE(2)
RGT E 7732-18-5 Water
CON room temperature

STAGE(3)
RCT CA 186692-68-2
RGT CG 603-32-7 Ph3As, CH 534-17-8 Cs2CO3
CAT 72287-26-4 Palladium, [1,1'-bis(diphenylphosphino-κP)ferrocene]dichloro-, (SP-4-2)-
SOL 68-12-2 DMF
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 2 minutes, room temperature
SUBSTAGE(3) room temperature
SUBSTAGE(4) 8 hours, room temperature

STAGE(4)
RGT BS 12125-02-9 NH4Cl
SOL 7732-18-5 Water
CON room temperature

PRO CE ***461044-42-8***

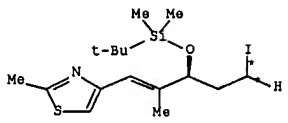
L33 ANSWER 8 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 139:197285 CASREACT Full-text
TITLE: A total synthesis of epothilones using solid-supported reagents and scavengers
AUTHOR(S): Storer, R. Ian; Takemoto, Toshiyasu; Jackson, Philip S.; Ley, Steven V.
CORPORATE SOURCE: University Chemical Laboratories, University of Cambridge, Cambridge, CB2 1EW, UK
SOURCE: Angewandte Chemie, International Edition (2003), 42(22), 2521-2525
CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



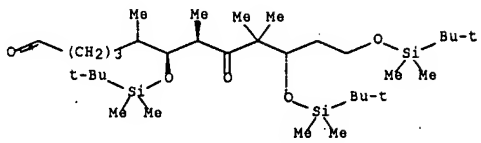
I

AB A total synthesis of epothilone C (I) with concomitant formal synthesis of epothilone A is described, using immobilized reagents and scavengers to effect multistep synthetic transformations and purifications.

RX(27) OF 210 ...T + BP ===> BQ...



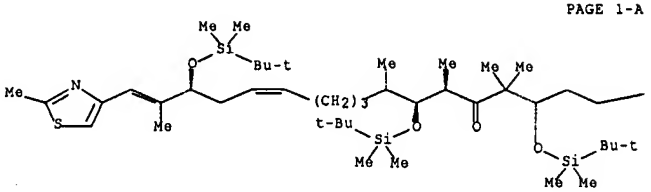
T
solid supporte
d



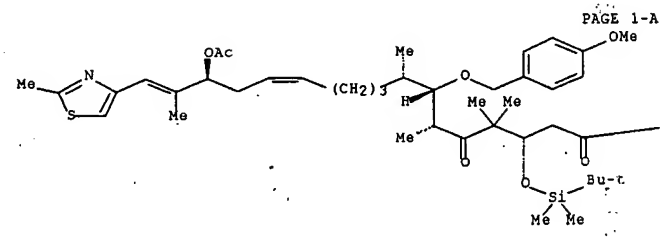
BP

(27)

PAGE 1-A



5
STEPS
→



PAGE 1-B

OBu-t

CE
YIELD 65%

RX(9) RCT AG ***247900-97-6***, AI 109-80-8

STAGE(1)
RGT AK 7550-45-0 TiCl4
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) room temperature -> -78 deg C
SUBSTAGE(4) 30 minutes

STAGE(2)
RGT J 144-55-8 NaHCO3
SOL 7732-18-5 Water

PRO AJ 461044-39-3

RX(25)

STAGE(1)

RGT BV 79-37-8 (COCl)2
SOL 75-09-2 CH2Cl2, 67-68-5 DMSO
CON SUBSTAGE(2) 30 minutes

STAGE(2)
RCT AJ 461044-39-3
SOL 75-09-2 CH2Cl2
CON SUBSTAGE(2) 3 hours

STAGE(3)
RGT AE 121-44-8 Et3N

PRO BU 461044-40-6

RX(26) RCT BX 184246-51-3

STAGE(1)
RGT BF 109-72-8 BuLi
SOL 109-99-9 THF
CON SUBSTAGE(2) 15 minutes

STAGE(2)
RCT BU 461044-40-6
CON SUBSTAGE(2) room temperature

STAGE(3)
RGT BS 12125-02-9 NH4Cl
SOL 7732-18-5 Water

PRO BY 461044-41-7

RX(27) RCT BY 461044-41-7

STAGE(1)
RGT CB 7616-83-3 Hg(ClO4)2, CC 471-34-1 CaCO3
SOL 7732-18-5 Water
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 2 hours, room temperature

STAGE(2)
SOL 60-29-7 Et2O
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 10 minutes, room temperature

STAGE(3)
RCT BZ 3020-28-8
RGT BG 680-31-9 HMPT, CD 1070-89-9 (Me3Si)2N.Na
SOL 109-99-9 THF
CON SUBSTAGE(3) room temperature
SUBSTAGE(4) 1 hour

STAGE(4)
RGT BS 12125-02-9 NH4Cl
SOL 7732-18-5 Water

PRO CA 186692-68-2

RX(28) RCT BT 461044-35-9

STAGE(1)

RX(14) RCT AS 863981-49-1

STAGE(1)
RGT AU 64-17-5 EtOH
CAT 24057-28-1 Pyridinium tosylate
SOL 64-17-5 EtOH
CON 65 deg C

STAGE(2)
RGT Q 79-37-8 (COCl)2, AV 67-68-5 DMSO
SOL 75-09-2 CH2Cl2
CON -78 deg C

STAGE(3)
RGT AW 121-44-8 Et3N
CON -78 deg C -> room temperature

PRO AT 688318-68-5
NTE Swern oxidn. in stage 2

RX(15) RCT AY 185148-95-2

STAGE(1)
RGT BA 4111-54-0 LiN(Pr-i)2
CON -78 deg C

STAGE(2)
RCT AT 688318-68-5
CON -78 deg C

PRO AZ ***688318-69-6***
NTE stereoselective

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 7 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 139:277113 CASREACT Full-text
TITLE: Synthesis of atorvastatin and epothilone synthons via 2-deoxyribose-5-phosphate aldolase-catalyzed asymmetric aldol condensation of aldehydes
INVENTOR(S): Wong, Chi-huey; Liu, Junjie; De Santis, Grace; Burk, Mark
PATENT ASSIGNEE(S): The Scripps Research Institute, USA; Diversa Corporation
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003077868	A2	20030925	WO 2003-US7982	20030314
WO 2003077868	A3	20040401		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

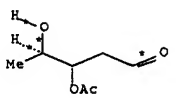
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2479247	A1	20030925	CA 2003-2479247	20030314
AU 2003225810	A1	20030929	AU 2003-225810	20030314
US 2003232416	A1	20031218	US 2003-390544	20030314
EP 1485498	A2	20041215	EP 2003-744689	20030314
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005520510	T	20050714	JP 2003-575922	20030314
US 2007015260	A1	20070118	US 2006-481653	20060705
PRIORITY APPLN. INFO.:			US 2002-364641P	20020314
			US 2003-390544	20030314
			WO 2003-US7982	20030314

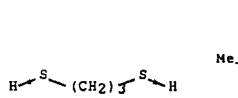
OTHER SOURCE(S): MARPAT 139:277113

AB The present invention is based on the discovery that 2-deoxyribose-5-phosphate aldolase (DERA, EC 4.1.2.4) and variants thereof can be used to catalyze sequential asym. aldol reactions between a wide variety of donor and acceptor aldehydes. The reaction products typically contain at least two new stereogenic centers and can be produced in enantiomerically pure form. As such, DERA catalyzed asym. aldol chemical can be exploited to produce synthons for the synthesis of a variety of bioactive mols., e.g. epothilone A.

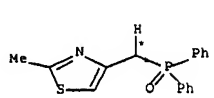
RX(147) OF 294 COMPOSED OF RX(9), RX(25), RX(26), RX(27), RX(28)
RX(147) ***AG*** + AI + BX + BZ + BT ===> ***CE***



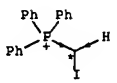
AG



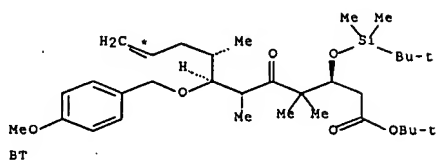
AI



BX



BZ

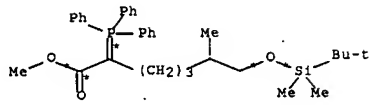


BT

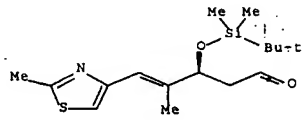
AB An efficient synthesis of the epothilone B derivative 26-fluoroepothilone B (I) was realized by early introduction of the synthetically demanding fluoromethyl epoxide function. The presence of a fluoro substituent results in a remarkable increase in the stability of the epoxide, which tolerates the wide range of reaction conditions required for the fragment coupling step and end game transformations.

RX(175) OF 310 COMPOSED OF RX(10), RX(24), RX(25), RX(26), RX(27), RX(14), RX(15)

RX(175) H + ***AG*** + BW + AY ===> ***AZ***

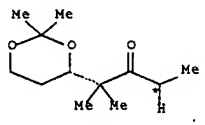


H



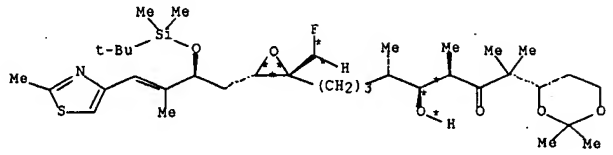
AG

BW



AY

7 STEPS



AZ
YIELD 77%

RX(10) RCT H 226940-40-5, AG ***188730-08-7***
PRO AH 226940-54-1
SOL 108-88-3 PhMe
CON 40 deg C
NTE stereoselective

RX(24) RCT AH 226940-54-1

STAGE(1)
RGT BY 76-05-1 F3CCO2H
SOL 109-99-9 THF, 7732-18-5 Water
CON 23 deg C

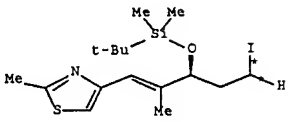
STAGE(2)
RCT BW 110-87-2
CAT 24057-28-1 Pyridinium tosylate
SOL 75-09-2 CH2Cl2
CON 23 deg C

PRO BX 688318-79-8

RX(25) RCT BX 688318-79-8
RGT AJ 1191-15-7 AlH(Bu-i)2
PRO BZ 688318-80-1
SOL 109-99-9 THF
CON SUBSTAGE(1) -78 deg C
SUBSTAGE(2) -78 deg C -> 0 deg C
NTE regioselective

RX(26) RCT BZ 688318-80-1
RGT AL 75-91-2 t-BuOOH
PRO CA 688318-81-2
CAT 546-68-9 Ti(OPr-i)4, 87-91-2 Di-Et L-tartrate
SOL 75-09-2 CH2Cl2
CON 2 hours, -30 deg C
NTE stereoselective, Katsuki-Sharpless epoxidn., mol. sieves used

RX(27) RCT CA 688318-81-2
RGT AR 38078-09-0 DAST [(Et2N).SF3]
PRO AS 863981-49-1
SOL 75-09-2 CH2Cl2
CON 23 deg C
NTE using Yarovenko or Ishikawa reagents gave comparable results



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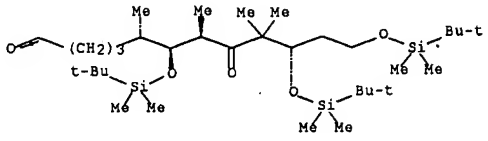
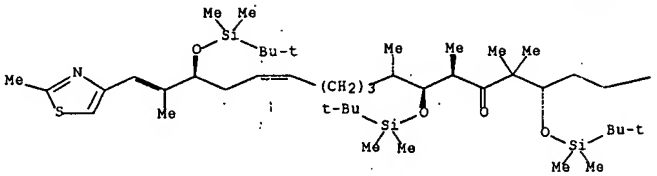


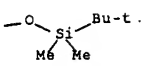
EH

2 STEPS

PAGE 1-A



PAGE 1-B



EI
YIELD 93%

RX(50) RCT N ***193146-30-4***
RGT O 603-35-0D PPh3
PRO EB 725738-64-7D
SOL 108-88-3 PhMe
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 18 hours, 90 deg C
SUBSTAGE(3) 90 deg C -> room temperature
NTE attachment to solid-supported reagent Fluka polymer bound triphenylphosphine

RX(54) RCT EB 725738-64-7D

STAGE(1)
RGT CY 1070-89-9 (Me3Si)2N.Na
SOL 109-99-9 THF
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 10 minutes, room temperature
SUBSTAGE(3) room temperature -> -78 deg C

STAGE(2)
RCT EH 346652-91-3
CON SUBSTAGE(1) 1 minute, -78 deg C
SUBSTAGE(2) 10 minutes, -78 deg C

PRO EI ***583829-96-3***
NTE solid-supported reactant
REFERENCE COUNT: 122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 6 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 140:423500 CASREACT Full-text
TITLE: Total synthesis of 26-fluoro-epothilone B
AUTHOR(S): Koch, Guido; Loiseleur, Olivier; Altmann, Karl-Heinz
CORPORATE SOURCE: Novartis Institutes for Biomedical Research, Basel, 4002, Switz.
SOURCE: Synlett (2004), (4), 693-697
CODEN: SYNLES; ISSN: 0936-5214
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
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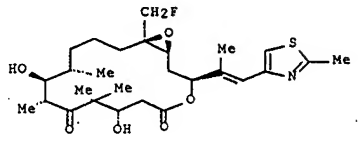

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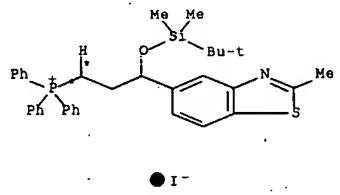
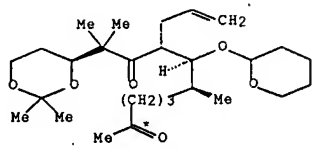
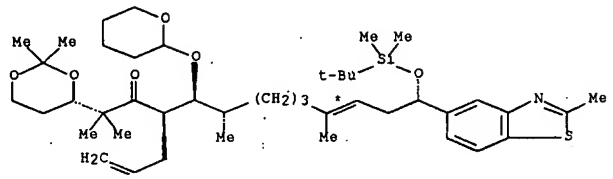


AE



AB

(6)



AF
YIELD 86%

RX(6) RCT AE ***823203-10-7***

STAGE(1)
SOL 109-99-9 THF
CON 23 deg C -> 0 deg C

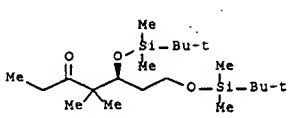
STAGE(2)
RGT AG 1070-89-9 (Me3Si)2N.Na
SOL 109-99-9 THF
CON 0 deg C

STAGE(3)
RCT AB 823203-08-3
SOL 109-99-9 THF
CON SUBSTAGE(1) 0 deg C
SUBSTAGE(2) 0 deg C -> 23 deg C
SUBSTAGE(3) 5 hours, 23 deg C

STAGE(4)
RGT R 12125-02-9 NH4Cl
SOL 7732-18-5 Water
CON 23 deg C

PRO AF ***823203-09-4***
NTE last stage quench
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 5 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 141:140221 CASREACT Full-text
TITLE: Multi-step application of immobilized reagents and scavengers: A total synthesis of epothilone C
AUTHOR(S): Storer, R. Ian; Takemoto, Toshiyasu; Jackson, Philip S.; Brown, Dearg S.; Baxendale, Ian R.; Ley, Steven V.
CORPORATE SOURCE: Department of Chemistry, University of Cambridge, Cambridge, CB2 1EW, UK
SOURCE: Chemistry--A European Journal (2004), 10(10), 2529-2547
CODEN: CEUJED; ISSN: 0947-6539
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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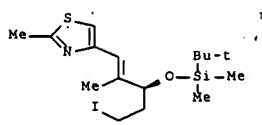


II

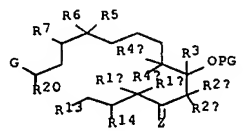
AB The total synthesis of the cytotoxic antitumor natural product epothilone C has provided a stage for the exploitation and further development of immobilized reagent methods. A stereoselective convergent synthetic strategy was applied, incorporating polymer-supported reagents, catalysts, scavengers and catch-and-release techniques to avoid frequent aqueous work-up and chromatog. purification The enantioselective preparation of 3 key fragments heptanone I, (S)-2-methyl-6-heptenal, and thiazole II along with their elaboration via diastereoselective coupling into epothilone C is presented.

RX(112) OF 662 COMPOSED OF RX(50), RX(54)
RX(112) ***N*** + EH ===> ***EI***

L33 ANSWER 4 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 142:113814 CASREACT Full-text
TITLE: Method for producing C1-C15 fragments of epothilones and derivatives thereof
INVENTOR(S): Klar, Ulrich; Buchmann, Bernd; Schwede, Wolfgang; Skuballa, Werner
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005003071	A1	20050113	WO 2004-EP6685	20040619
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10331004	A1	20050224	DE 2003-10331004	20030703
AU 2004254200	A1	20050113	AU 2004-254200	20040619
CA 2531078	A1	20050113	CA 2004-2531078	20040619
EP 1641734	A1	20060405	EP 2004-740122	20040619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
CN 1816514	A	20060809	CN 2004-80019005	20040619
BR 2004012179	A	20060822	BR 2004-12179	20040619
IN 2006DN00056	A	20070824	IN 2006-DN56	20060103
MX 2006PA00172	A	20060427	MX 2006-PA172	20060105
NO 2006000554	A	20060403	NO 2006-554	20060202
US 2007142675	A1	20070621	US 2006-563058	20060619
PRIORITY APPLN. INFO.:			DE 2003-10331004	20030703
			WO 2004-EP6685	20040619

OTHER SOURCE(S): MARPAT 142:113814
GI



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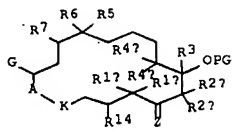
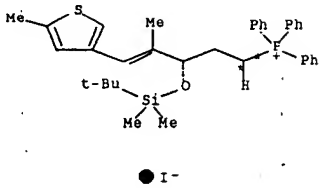


II

AB The invention relates to a method for preparing C1-C15 fragments I [R1a, R1b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R1aR1b = (CH2)m; m = 2 - 5; R2a, R2b = H, C1-10-alkyl, C2-10-alkenyl, C2-10-alkynyl, aryl, C7-20-aralkyl; R2aR2b = (CH2)n; n = 2 - 5; R3 = H, C1r10-alkyl, aryl, C7-20-aralkyl; R4a, R4b = = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4aR4b = (CH2)p; p = 2 - 5; R5 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R6, R7 = H; R6R7 = bond, O; G = X:CR8, bi- or tricyclic aryl; R8 = H, halogen, (un)substituted C1-20-alkyl, aryl, C7-20-aralkyl; X = O, (OR23)2, C2-10-alkylene- α,ω-dioxy, H(OR9), CR10R11; R23 = C1-20-alkyl; R9 = H, protecting group; R10, R11 = H, C1-10-alkyl, aryl, C7-20-aralkyl; CR10R11 = 5 - to 7-membered carbocycle; R13 = CH2OR13a, CH2-halo, CHO, CO2R13b, CO-halo; R13a, R14a = H, SO2alkyl, SO2-aryl, SO2-aralkyl; R13aR14a = (CH2)o, CR15aR15b; o = 2 - 4; R13b, R14b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R15a, R15b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R15aR15b = (CH2)q; q = 3 - 6; R20 = O-PG, NHR29, N3; Z = O, H(OR12); R12 = H, PG] of epothilones and derivs. The procedure comprises the bonding of a C1-C6 fragment, R13CH2CHR14CR1aR1bC(:O)CHR2aR2b, to a C7-C12 fragment, R5C(:V)(CH2)3CR4aR4bC(:W)R3a [V, W = O, (OR23)2, C2-10-alkylene- α,ω-dioxy, H(OR9)], to form a C1-C12 fragment, R5C(:V)(CH2)3CR4aR4bCR3a(O-PG14)CR2aR2bC(:Z)CR1aR1bCHR14CH2R13 [PG = H, protecting group], which is then treated with a C13-C15 fragment, G-CR20'CH2CHR7'R21 [R7' = H; R20' = halogen, N3, NHR29, OH, O-PG, NR29-PG, C1-20-(perfluoro)alkylsulfonyloxy, (C1-4-alkyl, NO2, Cl, Br-substituted) benzyloxy, NR29SO2Me, NR29C(:O)Me, CH2C(:O)Me; R21 = OH, halo, O-PG, P+Ph3Hal- (Hal = F, Cl, Br, I), P(O)(OQ)2 (Q = C1-10-alkyl, Ph), P(:O)Ph2; R29 = H, C1-6-alkyl], to form the C1-C15 epothilone intermediate product I. Thus, I [R1a = R1b = R5 = Me, R2a = CH2CH:CH2-β, R2b = R4b = H-α, R3 = H-β, R4a = Me-β, R6R7 = bond, R13 = CO2H, R14 = OSiMe2CMe3-β, R20 = OSiMe2CMe3-α, G = 2-methylbenzothiazol-5- yl, PG = SiMe2CMe3, Z = O] was prepared from (S)-4-(2-methyl-3-oxohept-6-en- 2-yl)-2,2-dimethyl-1,3-dioxane via lithiation and reaction with (2S,6RS)-2-methyl-6-[(tert-butyldimethylsilyl)oxy]heptanal, tetrahydropyranylation, desilylation with Bu4NF in THF, oxidation in CH2Cl2 containing N-methylmorpholine N-oxide and catalytic tetrapropylammonium perruthenate, Wittig reaction with [(3S)-3-(2-methylbenzothiazol-5- yl)propyl]triphenylphosphonium iodide, deisopropylidenation/detetrahydropy ranylation with catalytic 4-MeC6H4SO3H in EtOH, silylation with CF3SO2SiMe2CMe3, regioselective desilylation with (±)-camphor-10- sulfonic acid, Swern oxidation with DMSO/(COCl)2 in CH2Cl2 and carbonyl oxidation with NaOCl2 in aqueous THF/Me3COH. The produced C1-C15 epothilone intermediate products can be converted into the intrinsically active ingredients II [AK = OC(:O), OCH2, CH2C(:O), NR29C(:O), NR29SO2; R29 = H, C1-6-alkyl] according to known methods. The invention also relates to the corresponding C1-C12 fragments.

RX(6) OF 60 ...***AE*** + AB ===> ***AF***...



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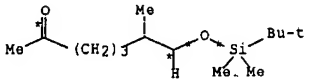

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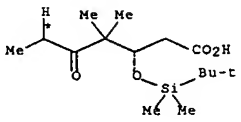

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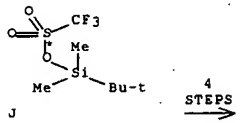
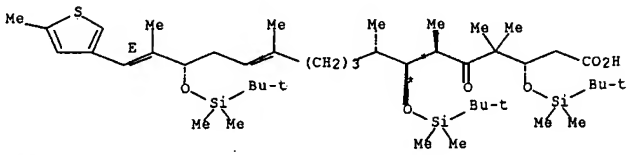


J

4 STEPS



CA
YIELD 31%

RX(22) RCT AV ***861124-76-7***

STAGE(1)
RGT BV 1070-89-9 (Me3Si)2N.Na
SOL 109-99-9 THF
CON 15 minutes, 0 deg C

STAGE(2)
RCT BS 190370-00-4
SOL 109-99-9 THF
CON 12 hours, -20 deg C

STAGE(3)
RGT M 12125-02-9 NH4Cl
SOL 7732-18-5 Water

PRO BU 861124-92-7

RX(23) RCT BU 861124-92-7

STAGE(1)
RGT BX 3144-16-9 10-CSA
SOL 67-56-1 MeOH, 75-09-2 CH2Cl2
CON SUBSTAGE(1) 5 minutes, 0 deg C
SUBSTAGE(2) 0.5 hours, 0 deg C
SUBSTAGE(3) 1 hour, 25 deg C

STAGE(2)
RGT BI 121-44-8 Et3N

PRO BW 861124-94-9

RX(24) RCT BW 861124-94-9

STAGE(1)
RGT BZ 26412-87-3 Pyridine-SO3 (1:1), BO 67-68-5 DMSO, BI 121-44-8 Et3N
SOL 75-09-2 CH2Cl2
CON 0.5 hours, 25 deg C

STAGE(2)
RGT M 12125-02-9 NH4Cl
SOL 7732-18-5 Water, 60-29-7 Et2O

PRO BY 861124-97-2

RX(25) RCT S 187283-45-0, BY 861124-97-2

STAGE(1)
RGT BZ 26412-87-3 Pyridine-SO3 (1:1), BO 67-68-5 DMSO, BI 121-44-8 Et3N
SOL 75-09-2 CH2Cl2
CON 0.5 hours, 25 deg C

STAGE(2)
RGT M 12125-02-9 NH4Cl
SOL 7732-18-5 Water, 60-29-7 Et2O

STAGE(3)
RCT J 69739-34-0
RGT L 108-48-5 2,6-Lutidine
SOL 75-09-2 CH2Cl2
CON 2 hours, 0 deg C

STAGE(4)
RGT BE 7647-01-0 HCl
SOL 7732-18-5 Water

STAGE(5)
RGT CB 584-08-7 K2CO3
CON 15 minutes, 25 deg C

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              CON  SUBSTAGE(1) 5 deg C
                   SUBSTAGE(2) 1 minute, 5 deg C

            STAGE(2)
               RCT  T 220775-18-8
               SOL  109-99-9 THF
               CON  5 hours

         PRO  BD 924727-13-9

RX(16)   RCT  BD 924727-13-9
         PRO  BF 279226-51-6
         CAT  104-15-4 TsOH
         SOL  64-17-5 EtOH
         CON  2 hours, room temperature

RX(17)

            STAGE(1)
               RGT  AF 67-68-5 DMSO, BH 79-37-8 (COCl)2
               SOL  75-09-2 CH2Cl2
               CON  SUBSTAGE(1) -78 deg C
                    SUBSTAGE(2) 10 minutes, -78 deg C

            STAGE(2)
               RCT  BF 279225-51-6
               SOL  75-09-2 CH2Cl2
               CON  30 minutes, -78 deg C

            STAGE(3)
               RGT  AG 121-44-8 Et3N
               CON  -78 deg C -> -10 deg C

         PRO  BG 279226-52-7
         NTE  Wittig reaction

RX(18)   RCT  BI 305840-13-5

            STAGE(1)
               RGT  BL 4111-54-0 LiN(Pr-i)2
               SOL  109-99-9 THF
               CON  SUBSTAGE(1) -70 deg C
                    SUBSTAGE(2) 10 minutes, -70 deg C
                    SUBSTAGE(3) 1 hour, -30 deg C
                    SUBSTAGE(4) -30 deg C -> -70 deg C

            STAGE(2)
               RGT  AL 7646-85-7 ZnCl2
               SOL  109-99-9 THF
               CON  SUBSTAGE(1) -70 deg C
                    SUBSTAGE(2) 10 minutes, -70 deg C
                    SUBSTAGE(3) 15 minutes, -70 deg C

            STAGE(3)
               RCT  BG 279226-52-7
               SOL  109-99-9 THF
               CON  SUBSTAGE(1) 30 minutes, -70 deg C
                    SUBSTAGE(2) 3.5 hours, -70 deg C

            STAGE(4)
```



```
               RCT  BJ 69739-34-0

         PRO  BK 924727-14-0
REFERENCE COUNT:          39    THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
                                RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33  ANSWER 3 OF 23  CASREACT  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         143:172686  CASREACT  Full-text
TITLE:                    New method for totally synthesizing natural product-
                          epothilones
INVENTOR(S):              Yan, Jiaqi
PATENT ASSIGNEE(S):       Peop. Rep. China
SOURCE:                   Faming Zhuanli Shenqing Gongkai Shuomingshu, 29 pp.
                          CODEN: CNXXEV
DOCUMENT TYPE:            Patent
LANGUAGE:                 Chinese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
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     CN 1418881         A    20030521      CN 2002-153675   20021205
PRIORITY APPLN. INFO.:                     CN 2002-153675   20021205
GI
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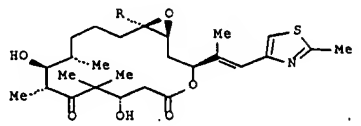

I

AB The invention discloses a novel multi-step synthetic method for preparing Epothilone A and epothilone B (I; R = H or Me resp.) in a convergent approach starting from 2,2-dimethyl-3-oxopentanal, propionaldehyde SAMP hydrazone, and Et 2-methylthiazolidin-4-ylcarboxylate.

```
RX(97) OF 191 COMPOSED OF RX(22), RX(23), RX(24), RX(25)
RX(97)    AV  +  BS  +  S  +  J  ===>  CA
```

STAGE(2)
RCT P 865535-39-3
RGT V 534-17-8 Cs2CO3
CAT 603-32-7 Ph3As, 72287-26-4 Palladium, [1,1'-bis(diphenylphosphino-κP)ferrocene]dichloro-, (SP-4-2)-
SOL 68-12-2 DMF
CON 2 hours, 0 deg C -> room temperature

PRO T 865535-59-7

RX(11) RCT T 865535-59-7
RGT AQ 1310-65-2 LiOH
PRO AP ***865535-60-0***
SOL 7732-18-5 Water, 67-63-0 Me2CHOH
CON 2.5 hours, 60 deg C

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 146:229070 CASREACT Full-text
TITLE: Total synthesis and antitumor activity of ZK-EPO: The first fully synthetic epothilone in clinical development
AUTHOR(S): Klar, Ulrich; Buchmann, Bernd; Schwede, Wolfgang; Skuballa, Werner; Hoffmann, Jens; Lichtner, Rosemarie B.
CORPORATE SOURCE: Schering AG, Research Center Eurpoe, Berlin, Germany
SOURCE: Angewandte Chemie, International Edition (2006), 45(47), 7942-7948
CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
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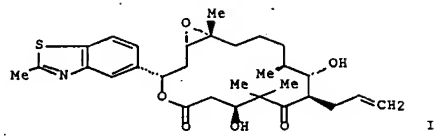
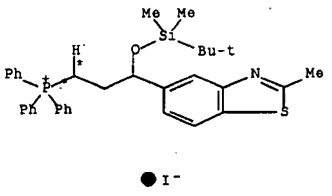


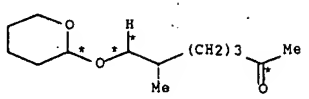
I

AB From about 350 active epothilone analogs synthesized by a highly convergent synthesis, ZK-EPO (I) was chosen for clin. development on the basis of its outstanding preclin. data. This compound exhibits higher activity and efficacy than taxanes, such as paclitaxel and second-generation epothilones, a fast and efficient cellular uptake, no recognition by efflux mechanisms, and an improved therapeutic window.

RX(84) OF 314 COMPOSED OF RX(15), RX(16), RX(17), RX(18)
RX(84) ***BC*** + T + BI + BJ ===> ***BK***



BC



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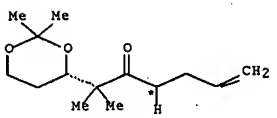
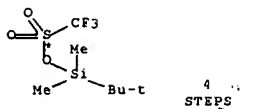
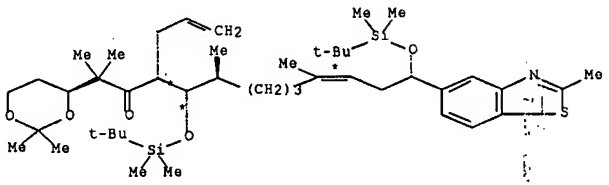


BI



BJ

4 STEPS



BK
YIELD 73%

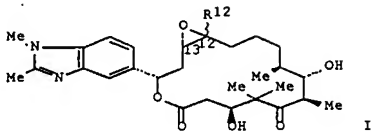
RX(15) RCT BC ***823203-10-7***

STAGE(1)
RGT BE 1070-89-9 (Me3Si)2N.Na
SOL 109-99-9 THF

100.0% DONE 3173 VERIFIED 468 HIT RXNS 23 DOCS
SEARCH TIME: 00.00.04

=> d ibib abs fhit L33 1-23

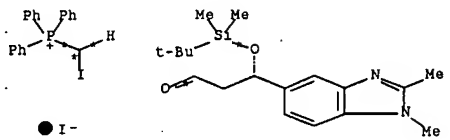
L33 ANSWER 1 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 146:251631 CASREACT Full-text
TITLE: Total synthesis and biological assessment of benzimidazole-based analogs of epothilone A: Ambivalent effects on cancer cell growth inhibition
AUTHOR(S): Cachoux, Frederic; Isarno, Thomas; Wartmann, Markus; Altmann, Karl-Heinz
CORPORATE SOURCE: Prestwick Chemical, Illkirch, Fr.
SOURCE: ChemBioChem (2006), 7(1), 54-57
CODEN: CBCHFX; ISSN: 1439-4227
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



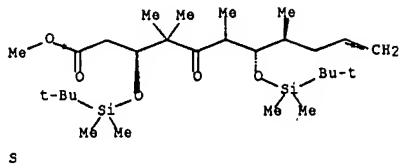
I

AB The title (12R,13S)- and (12S,13S)-epoxy-benzimidazole epothilone derivs. I (R12 = β-, α-H, resp.), as well as the corresponding (12Z)- and (12E)-Δ12-olefin epoxide precursors, were prepared and evaluated for inhibition of growth of human cancer cell lines, such as KB-31 and KB-8511.

RX(30) OF 64 COMPOSED OF RX(10), RX(3), RX(4), RX(11)
RX(30) AN + ***AC*** + S ===> ***AP***

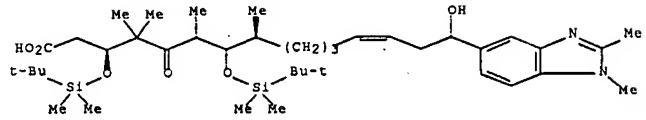


AN AC



S

4 STEPS



AP
YIELD 87%

RX(10) RCT AN 3020-28-8

STAGE(1)
RGT AO 1070-89-9 (Me3Si)2N.Na
SOL 109-99-9 THF
CON 15 minutes, room temperature

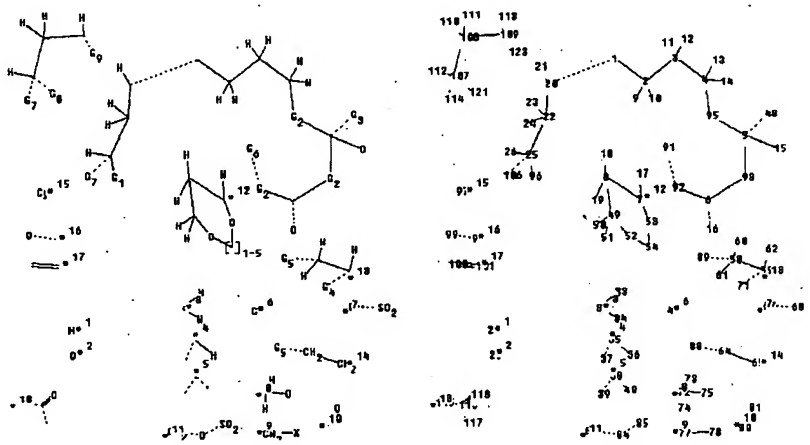
STAGE(2)
RCT AC ***279226-82-3***
CON 30 minutes, -78 deg C

PRO O 865535-38-2
NTE stereoselective, Wittig reaction

RX(3) RCT O 865535-38-2
RGT Q 3144-16-9 10-CSA
PRO P 865535-39-3
SOL 67-56-1 MeOH, 75-09-2 CH2Cl2
CON 17 hours, room temperature

RX(4) RCT S 279227-12-2

STAGE(1)
RGT U 280-64-8 9-BBN
SOL 109-99-9 THF
CON 90 minutes, room temperature



chain nodes :
2 3 4 5 9 10 11 12 13 14 15 17 18 19 21 22 23 24 25 26 27 28
32 33 34 36 48 50 51 58 59 60 61 62 64 65 67 68 71 72 73 74 75
77 78 80 81
83 84 85 88 89 91 92 93 95 96 97 101 106 107 108 109 110 111 112
113 114 115
116 117 118 121 123
ring nodes :
7 8 49 52 53 54
ring/chain nodes :
1 6 16 20 35 37 38 39 40 45 98 99 100
chain bonds :
1-2 2-3 2-9 2-10 3-4 3-11 3-12 4-14 4-13 4-95 5-93 5-48 5-15 5-95 6-92
6-93 7-17 8-18 8-19 20-21 20-22 22-23 22-24 22-25 25-26 25-96 25-106
32-33 32-34
35-36 49-50 49-51 58-59 58-60 58-61 58-89 59-62 59-71 64-65 64-88 67-68
72-73 72-74
72-75 77-78 80-81 83-84 84-85 91-92 100-101 107-108 107-112 107-114 107-121 108-109 108-110
108-111 109-113 109-123 115-116 116-117 116-118
ring/chain bonds :
1-20 6-16 35-37 38-39 38-40 98-99
ring bonds :
7-8 7-53 8-49 49-52 52-54 53-54
exact/norm bonds :
1-2 1-20 2-3 3-4 4-95 5-93 5-48 5-15 5-95 6-92 6-16 6-93 7-8 7-53 8-49
20-22 22-25 25-96 25-106 35-37 38-39 38-40 49-52 52-54 53-54 58-89 59-71
64-88 67-68
72-75 80-81 83-84 84-85 91-92 98-99 107-114 107-121 109-123 115-116 116-117 116-118

exact bonds :
2-9 2-10 3-11 3-12 4-14 4-13 7-17 8-18 8-19 20-21 22-23 22-24 25-26
32-33 32-34 35-36 49-50 49-51 58-59 58-60 58-61 59-62 64-65 72-73 72-74
77-78 100-101
107-108 107-112 108-109 108-110 108-111 109-113

G1:[*1],[*2]

G2:[*3],[*4],[*5]

G3:H,[*6]

G4:X,OH,O,[*7]

G5:[*8],[*9],[*10],[*11]

G6:[*12],[*13],[*14]

G7:[*15],[*16],[*17]

G8:O,N,X,[*18]

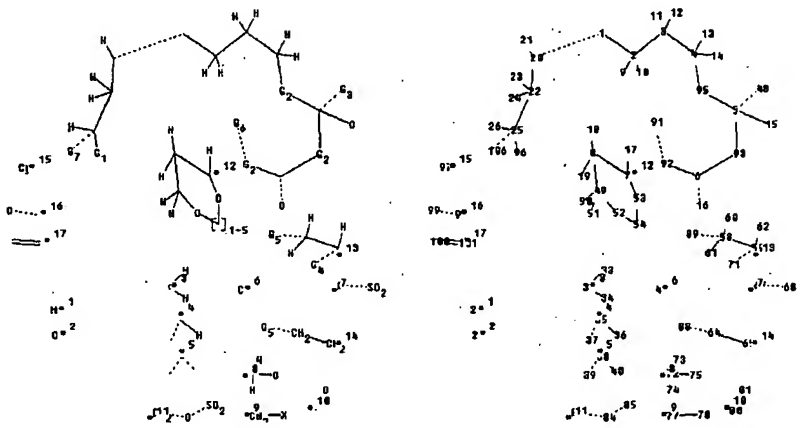
G9:O,P,X

Match level :
1:CLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS
10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS
18:CLASS 19:CLASS
20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS
28:CLASS 32:CLASS
33:CLASS 34:CLASS 35:CLASS 36:CLASS 37:CLASS 38:CLASS 39:CLASS 40:CLASS
45:CLASS 48:CLASS
49:Atom 50:CLASS 51:CLASS 52:Atom 53:Atom 54:Atom 58:CLASS 59:CLASS
60:CLASS 61:CLASS
62:CLASS 64:CLASS 65:CLASS 67:CLASS 68:CLASS 71:CLASS 72:CLASS 73:CLASS
74:CLASS 75:CLASS
77:CLASS 78:CLASS 80:CLASS 81:CLASS 83:CLASS 84:CLASS 85:CLASS 88:CLASS
89:CLASS 91:CLASS
92:CLASS 93:CLASS 95:CLASS 96:CLASS 97:Atom 98:CLASS 99:CLASS 100:CLASS
101:CLASS 106:CLASS
107:CLASS 108:CLASS 109:CLASS 110:CLASS 111:CLASS 112:CLASS 113:CLASS
114:CLASS 115:CLASS
116:CLASS 117:CLASS 118:CLASS 121:CLASS 123:CLASS
Generic attributes :
97:
Saturation : Unsaturated
Type of Ring System : Polycyclic

fragments assigned product role:
containing 1
fragments assigned reactant/reagent role:
containing 107
node mappings:
22:108

L33 23 SEA FILE=CASREACT SUB=L30 SSS FUL L31 (468 REACTIONS)

Structure attributes must be viewed using STN Express query preparation:
Uploading L1b.str



chain nodes :
2 3 4 5 9 10 11 12 13 14 15 17 18 19 21 22 23 24 25 26 27 28
32 33 34 36 48 50 51 58 59 60 61 62 64 65 67 68 71 72 73 74 75
77 78 80 81
83 84 85 88 89 91 92 93 95 96 97 101 106
ring nodes :
7 8 49 52 53 54
ring/chain nodes :
1 6 16 20 35 37 38 39 40 45 98 99 100
chain bonds :
1-2 2-3 2-9 2-10 3-4 3-11 3-12 4-14 4-13 4-95 5-93 5-48 5-15 5-95 6-92
6-93 7-17 8-18 8-19 20-21 20-22 22-23 22-24 22-25 25-26 25-96 25-106
32-33 32-34
35-36 49-50 49-51 58-59 58-60 58-61 58-89 59-62 59-71 64-65 64-88 67-68
72-73 72-74
72-75 77-78 80-81 83-84 84-85 91-92 100-101
ring/chain bonds :
1-20 6-16 35-37 38-39 38-40 98-99
ring bonds :
7-8 7-53 8-49 49-52 52-54 53-54
exact/norm bonds :
1-2 1-20 2-3 3-4 4-95 5-93 5-48 5-15 5-95 6-92 6-16 6-93 7-8 7-53 8-49
20-22 22-25 25-96 25-106 35-37 38-39 38-40 49-52 52-54 53-54 58-89 59-71
64-88 67-68
72-75 80-81 83-84 84-85 91-92 98-99
exact bonds :
2-9 2-10 3-11 3-12 4-14 4-13 7-17 8-18 8-19 20-21 22-23 22-24 25-26
32-33 32-34 35-36 49-50 49-51 58-59 58-60 58-61 59-62 64-65 72-73 72-74

77-78 100-101

G1:[*1],[*2]

G2:[*3],[*4],[*5]

G3:H,[*6]

G4:X,OH,O,[*7]

G5:[*8],[*9],[*10],[*11]

G6:[*12],[*13],[*14]

G7:[*15],[*16],[*17]

Match level :
1:CLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS
10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS
18:CLASS 19:CLASS
20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS
28:CLASS 32:CLASS
33:CLASS 34:CLASS 35:CLASS 36:CLASS 37:CLASS 38:CLASS 39:CLASS 40:CLASS
45:CLASS 48:CLASS
49:Atom 50:CLASS 51:CLASS 52:Atom 53:Atom 54:Atom 58:CLASS 59:CLASS
60:CLASS 61:CLASS
62:CLASS 64:CLASS 65:CLASS 67:CLASS 68:CLASS 71:CLASS 72:CLASS 73:CLASS
74:CLASS 75:CLASS
77:CLASS 78:CLASS 80:CLASS 81:CLASS 83:CLASS 84:CLASS 85:CLASS 88:CLASS
89:CLASS 91:CLASS
92:CLASS 93:CLASS 95:CLASS 96:CLASS 97:Atom 98:CLASS 99:CLASS 100:CLASS
101:CLASS 106:CLASS

Generic attributes :
97:
Saturation : Unsaturated
Type of Ring System : Polycyclic

L3 560 SEA FILE=REGISTRY SSS FUL L1
L30 69 SEA FILE=CASREACT ABB=ON PLU=ON L3
L31 STR

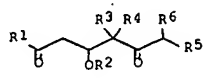
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation:
Uploading L31b.str

AT 368036	T	20070815	AT 1998-946309		19980810
US 2003144523	A1	20030731	US 2000-485292		20000503
PRIORITY APPLN. INFO.:			DE 1997-19735574	A	19970809
			DE 1997-19735575	A	19970809
			DE 1997-19735578	A	19970809
			DE 1997-19748928	A	19971024
			DE 1997-19749717	A	19971031
			DE 1997-19751200	A	19971113
			DE 1998-19813821	A	19980320
			WO 1998-EP5064	W	19980810

OTHER SOURCE(S): CASREACT 130:168162; MARPAT 130:168162

GI



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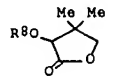

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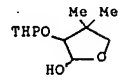
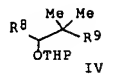


III



IV

AB Compds. I (R1 = H, OH, OR7; R2 = H, protective group; R3, R4 = H, C1-10-alkyl, C7-10-aralkyl; R3R4 = (CH2)m; R5, R6 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R7 = C1-20-alkyl, C7-20-aralkyl; R1 ≠ OH, when R2 = SiMe2CMe3, R3 = R4 = R5 = Me, R6 = H), useful for the preparation of epothilone and epothilone derivs., are prepared from (R)-, (S)- or (±)-pantolactone (II; R8 = H) via tetrahydropyranylation with 3,4-dihydro-2H-pyran and pyridinium p-toluenesulfonate and reduction of THP ether II (R8 = THP) with DIBAL-H, Wittig reaction of lactol III with MePh3P+Br-/BuLi, oxidation of pentenol IV (R9 = CH:CH2, R10 = CH2OH) with (COCl)2/DMSO in CH2Cl2, addition of an organometallic compound, R5CH2Y (Y = Li, MgX, X = Cl, Br, I), to aldehyde IV (R9 = CH:CH2, R10 = CHO), hydroboration and oxidation of hexenol IV [R9 = CH:CH2, R10 = CH(OH)CH2R5] with N-methylmorpholine N-oxide/TPAP and oxidation of keto aldehyde IV (R9 = CH2CHO, R10 = COCH2R5) to keto acid IV (R9 = CH2CO2H, R10 = COCH2R5) or hexenol IV [R9 = CH:CH2, R10 = CH(OH)CH2R5] can be oxidized then alkylated with LiN(CHMe2)2 and R6Z (Z = leaving group) and the resulting ketone IV [R9 = CH:CH2, R10 = COCHR5R6], can hydroborated and oxidized as above, leading to I.


```
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STRUCTURE FILE UPDATES:   10 OCT 2007  HIGHEST RN 950149-06-1
DICTIONARY FILE UPDATES:  10 OCT 2007  HIGHEST RN 950149-06-1

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=> file casreact
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FILE CONTENT:1840 - 6 Oct 2007 VOL 147 ISS 16

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************************************************************
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*                                                          *
************************************************************

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database compiled under the direction of Professor Dr. Klaus Kieslich.

This file contains CAS Registry Numbers for easy and accurate substance
identification.

=> d stat que L33
L1              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *
```

protecting group; R11 = H, protecting group] including all the stereoisomers and their mixts. are prepared E.g., title compound (S)-III [R5 = R6 = Me, R9 = R11 = H, R10 = TBDPS] was prepared in 6 steps from D-(-)-pantolactone via reaction with 3,4-dihydro-2H-pyran, hydride reduction, Wittig reaction with methyltriphenylphosphonium bromide, protection of OH with TBDPS-Cl, de-tetrahydropyranyl, and reduction with borane-THF.

L102 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:116658 CAPLUS Full-text
DOCUMENT NUMBER: 130:168163
TITLE: New (C13-C15)-fragments, method for their preparation and their application for synthesis of epothilone and epothilone derivatives
INVENTOR(S): ***Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd;*** Schirner, Michael
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 14 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19735575	A1	19990211	DE 1997-19735575	19970809
CA 2299608	A1	19990218	CA 1998-2299608	19980810
WO 9907692	A2	19990218	WO 1998-EP5064	19980810
WO 9907692	A3	19990514		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9893409	A	19990301	AU 1998-93409	19980810
EP 1005465	A2	20000607	EP 1998-946309	19980810
EP 1005465	B1	20070725		
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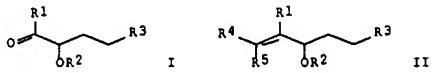
JP 2001512723	T	20010828	JP 2000-506196	19980810
AT 368036	T	20070815	AT 1998-946309	19980810
US 2003144523	A1	20030731	US 2000-485292	20000503

PRIORITY APPLN. INFO.:

DE 1997-19735574	A	19970809
DE 1997-19735575	A	19970809
DE 1997-19735578	A	19970809
DE 1997-19748928	A	19971024
DE 1997-19749717	A	19971031
DE 1997-19751200	A	19971113
DE 1998-19813821	A	19980320
WO 1998-EP5064	W	19980810

OTHER SOURCE(S): CASREACT 130:168163; MARPAT 130:168163
GI



AB The title compds. [I; II; R1 = H, alkyl, aryl, aralkyl; R2 = H, protecting group; R3 = OH, halo, OR6; R6 = protecting group; R4 = H, alkyl; R5 = H, alkyl, aryl, aralkyl] are prepared E.g., title compound I [R1 = Me, R2 = TBDPS, R3 = TBDMS] was prepared in 6 steps from L-(-)-malic acid via cyclization, 3-O-protection of 3(S)-hydroxy-2-tetrahydrofuranone, hydride reduction, ring opening and chain lengthening, 1-O-protection of 3(S)-(tert-butyldiphenylsilyloxy)-1,4-pentanediol, and oxidation of 3(S)-(tert-butyldiphenylsilyloxy)-5-(tert-butyldimethylsilyloxy)-2- pentanol. This was further treated with Et (2-methyl-4- thiazolylmethyl)phosphonate in THF-hexane containing BuLi to give (E,3S)-1-[[dimethyl(1,1-dimethylethyl)silyl]oxy]-3-[[(1,1- dimethylethyl)diphenylsilyl]oxy]-4-methyl-4-(2-methylthiazol-4-yl)pent-4- ene.

L102 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:116657 CAPLUS Full-text
DOCUMENT NUMBER: 130:168162
TITLE: New method for the preparation of the C(1)-C(6)-segment of epothilone and epothilone derivatives
INVENTOR(S): ***Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd;*** Schirner, Michael
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 12 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19735574	A1	19990211	DE 1997-19735574	19970809
CA 2299608	A1	19990218	CA 1998-2299608	19980810
WO 9907692	A2	19990218	WO 1998-EP5064	19980810
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W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9893409	A	19990301	AU 1998-93409	19980810
EP 1005465	A2	20000607	EP 1998-946309	19980810
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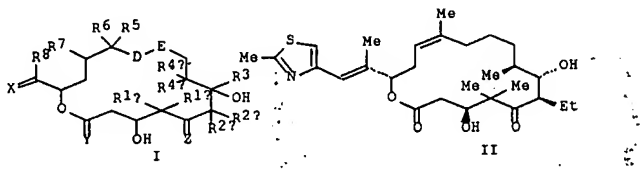
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, AL, MK				
JP 2001512723	T	20010828	JP 2000-506196	19980810

	DE 1998-19813821	A	19980320
	WO 1998-EP5064	W	19980810

OTHER SOURCE(S): MARPAT 130:196529
GI



I II

AB Epothilone derivs. of formula I [X = O, alkylene-α,ω-dioxy, two alkoxy groups, etc.; Y = O, H2; Z = O, (H, OH), (H, protected OH); R1a, R1b = H, alkyl, aryl, aralkyl, or together = (CH2)m where m = 2, 3, 4, 5; R2a, R2b = H, alkyl, aryl, aralkyl, or together = (CH2)n where n = 2, 3, 4, 5; when D-E = CH2CH2 or when Y = O, R2a or R2b may not be H/Me; R3 = H, alkyl, aryl, aralkyl; R4a, R4b = H, alkyl, aryl, aralkyl, or together = (CH2)p where p = 2, 3, 4, 5; D-E = CH2CH2, CH:CH, C.tplbond.C, 2,3-oxiranediyl, CH(OH)CH(OH), CH(OH)CH2; R5 = H, alkyl, aryl, aralkyl; R6, R7 = H, together = a saturated bond or O; R8 = H, alkyl, aryl, aralkyl all of which may be substituted] are prepared Thus, the title compds. (4S,7R,8S,9S,13E,16S(E))- and (4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-7- ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethylcyclohexadec-13-en-2,6-dione (II) were prepared in many steps. The new compds. interact with tubulin by stabilizing formed microtubuli. They are capable of influencing cell division in a phase-specific manner and are suitable for the treatment of malignant tumors, such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant melanoma, and acute lymphocytic and myelocytic leukemia. They are also suited for anti-angiogenesis therapy and for the treatment of chronic inflammatory diseases (psoriasis, arthritis). To prevent uncontrolled cell growth on, and for better tolerability of, medical implants, the derivs. can be introduced into or applied to polymeric materials. The compds. provided for in the invention can be used alone or, to achieve additive or synergistic effects, in combination with other principles and substance categories used in tumor therapy.

L102 ANSWER 22 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:116659 CAPLUS Full-text
DOCUMENT NUMBER: 130:168164
TITLE: New (C1-C6)-fragments, method for their preparation and their application for synthesis of epothilone and epothilone derivatives
INVENTOR(S): ***Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd;*** Schirner, Michael
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 18 pp.

CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19735578	A1	19990211	DE 1997-19735578	19970809
CA 2299608	A1	19990218	CA 1998-2299608	19980810
WO 9907692	A2	19990218	WO 1998-EP5064	19980810
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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9893409	A	19990301	AU 1998-93409	19980810
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EP 1005465	B1	20070725		
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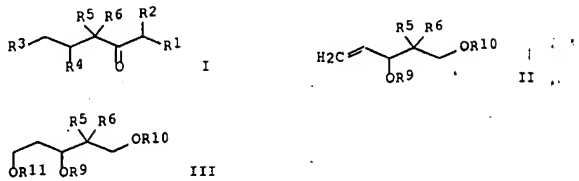
JP 2001512723	T	20010828	JP 2000-506196	19980810
AT 368036	T	20070815	AT 1998-946309	19980810
US 2003144523	A1	20030731	US 2000-485292	20000503

PRIORITY APPLN. INFO.:

DE 1997-19735574	A	19970809
DE 1997-19735575	A	19970809
DE 1997-19735578	A	19970809
DE 1997-19748928	A	19971024
DE 1997-19749717	A	19971031
DE 1997-19751200	A	19971113
DE 1998-19813821	A	19980320
WO 1998-EP5064	W	19980810

OTHER SOURCE(S): CASREACT 130:168164; MARPAT 130:168164
GI



I II III

AB The title compds. [I; II; III; R1, R2 = H, alkyl, aryl, aralkyl; R3 = CH2OH, CH2OR; R4 = OH, OR; R = CR7R8; R7, R8 = H, alkyl, aryl, or R7R8 = (CH2)n; n = 2-6; R5, R6 = H, alkyl, aralkyl, or R5R6 = (CH2)m; m = 2-5; R9, R10 = H,

from which structure-activity- relationships can be deduced. Epothilone A (R=H) Epothilone B (R=Me) Epothilone C (R=H) Epothilone D (R=Me).

L102 ANSWER 20 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:15195 CAPLUS Full-text
DOCUMENT NUMBER: 132:64110
TITLE: The preparation process, intermediate products and pharmaceutical use of epothilone derivatives
INVENTOR(S): ***Buchmann, Bernd; Klar, Ulrich; Skuballa, Werner; Schwede, Wolfgang;*** Schirner, Michael; Menrad, Andreas
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000000485	A1	20000106	WO 1999-EP4915	19990630
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19830060	A1	20000210	DE 1998-19830060	19980630
DE 19923001	A1	20001116	DE 1999-19923001	19990513
AU 9950369	A	20000117	AU 1999-50369	19990630

PRIORITY APPLN. INFO.:			
	DE 1998-19830060	A	19980630
	DE 1999-19923001	A	19990513
	WO 1999-EP4915	W	19990630

OTHER SOURCE(S): CASREACT 132:64110; MARPAT 132:64110
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to new epothilone derivs. I [R1a, R1b = H, C1-10-alkyl, aryl, C7-10-aralkyl; R1aR1b = (CH2)m, m = 2 - 5; R2a, R2b = H, C1-10-alkyl, aryl, C7-10-aralkyl; R2aR2b = (CH2)n, n = 2 - 5; R3 = H, C1-10-alkyl, aryl, C7-10-aralkyl; R4a, R4b = H, C1-10-alkyl, aryl, C7-10-aralkyl; R4aR4b = (CH2)m, m = 2 - 5; D-E = CH2CH2, CH:CH, C.tplbond.C, oxirane ring, CH(OH)CH(OH), CH(OH)CH2; R5 = C1-10-alkyl, aryl, C7-10-aralkyl; R6, R7 = H; R6R7 = O, bond; R8 = C1-10-alkyl, aryl, C7-10-aralkyl; R25 = H, C1-10-alkyl, C1-10-hydroxyalkyl, C1-10-haloalkyl; X = O, (OR9)2, C2-10-alkylene-α,ω-dioxy, CR11R12; CX = CH(OR10); R9 = C1-20-alkyl; R10 = H, protecting group; R11, R12 = H, C1-10-alkyl, aryl, C7-10-aralkyl; R11R12 = CH2, C5-7-carbocyclic ring; Y = O, CY = CH2; CZ = CH(OR13), R13 = H, protecting group] which are prepared via cyclization of ketones II [R15 = H, OH halogen, OR15a, OSO2R15b; R15a = H, SO2-alkyl, SO2-aryl, SO2-aralkyl, (CH2)o, CR16aR16b; R15b = H, C1-20-alkyl, aryl, C7-20-aralkyl; R16a, R16b = H, C1-10-alkyl, aryl, C7-20-aralkyl;

R16aR16b = (CH2)q; o = 2 - 4; q = 3 - 6]. Thus, epothilone derivative III was prepared via macrolactonization of carboxylic acid IV with 2,4,6-trichlorobenzoyl chloride and Et3N in THF followed by deprotection with aqueous CF3CO2H in CH2Cl2. I cooperate with tubulin by stabilizing formed microtubuli.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L102 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:126888 CAPLUS Full-text
DOCUMENT NUMBER: 130:196529
TITLE: Preparation of new epothilone derivatives as pharmaceutical agents
INVENTOR(S): ***Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd;*** Schirner, Michael
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 185 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9907692	A2	19990218	WO 1998-EP5064	19980810
WO 9907692	A3	19990514		
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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
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DE 19735575	A1	19990211	DE 1997-19735575	19970809
DE 19735578	A1	19990211	DE 1997-19735578	19970809
DE 19748928	A1	19990429	DE 1997-19748928	19971024
DE 19749717	A1	19990506	DE 1997-19749717	19971031
DE 19751200	A1	19990520	DE 1997-19751200	19971113
DE 19813821	A1	19990923	DE 1998-19813821	19980320
CA 2299608	A1	19990218	CA 1998-2299608	19980810
AU 9893409	A	19990301	AU 1998-93409	19980810
EP 1005465	A2	20000607	EP 1998-946309	19980810
EP 1005465	B1	20070725		
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JP 2001512723	T	20010828	JP 2000-506196	19980810
ZA 9810403	A	20000515	ZA 1998-10403	19981113
IN 190805	A1	20030823	IN 1998-DE3413	19981116
US 2003144523	A1	20030731	US 2000-485292	20000503
IN 2002DE01305	A	20050311	IN 2002-DE1305	20021227

PRIORITY APPLN. INFO.:			
	DE 1997-19735574	A	19970809
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	DE 1997-19748928	A	19971024
	DE 1997-19749717	A	19971031
	DE 1997-19751200	A	19971113

stabilizing the microtubuli which are formed. They are able to influence the cell division phase-specifically and are suitable for treating malignant tumors such as cancers of the ovaries, stomach, colon, glands, breasts, lungs, head and neck, malignant melanoma and acute lymphocytic and myelocytic leukemia. These compds. are also suitable for anti-angiogenesis therapy and for treating chronic inflammatory diseases (psoriasis, arthritis) and can be deposited on or in polymer materials in order to prevent uncontrolled cell proliferations on medical implants and to improve the compatibility. These derivs. can be used alone or in combination with other principles and classes of substances that can be used in the therapy of tumors to achieve additive or synergistic effects.

L102 ANSWER 18 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:573798 CAPLUS Full-text
DOCUMENT NUMBER: 133:177064
TITLE: Preparation of epothilone derivatives useful as pharmaceuticals
INVENTOR(S): ***Klar, Ulrich; Skuballa, Werner; Buchmann, Bernd; Schwede, Wolfgang;*** Schirner, Michael
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: PCT Int. Appl., 141 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000047584	A2	20000817	WO 2000-EP1104	20000211
WO 2000047584	A3	20001228		
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19907480	A1	20000817	DE 1999-19907480	19990211
CA 2360952	A1	20000817	CA 2000-2360952	20000211
EP 1161430	A2	20011212	EP 2000-920433	20000211
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BR 2000008206	A	20020219	BR 2000-8206	20000211
HU 200105330	A2	20020529	HU 2001-5330	20000211
JP 2002536450	T	20021029	JP 2000-598504	20000211
EE 200100422	A	20021216	EE 2001-422	20000211
IN 2001MN00825	A	20070504	IN 2001-MN825	20010713
BG 105803	A	20020329	BG 2001-105803	20010809
NO 2001003900	A	20011011	NO 2001-3900	20010810
MX 2001PA08148	A	20030721	MX 2001-PA8148	20010810
ZA 2001007458	A	20021210	ZA 2001-7458	20010910
US 7001916	B1	20060221	US 2001-913163	20011207
US 2006040990	A1	20060223	US 2005-189787	20050727

PRIORITY APPLN. INFO.:
DE 1999-19907480 A 19990211
DE 1999-19954229 A 19991104
WO 2000-EP1104 W 20000211

US 2001-913163 A3 20011207

OTHER SOURCE(S): MARPAT 133:177064
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Novel epothilone derivs. I (R4 = R5 = H, C1-C10 alkyl, aryl, C7-C20 aralkyl; R6, R7 are each H, or together an addnl. bond or O; R8 = Me or H; R1a, R1b together = trimethylene; R2 = Ph, CH2Ph; X = 2-pyridyl, 2-methyl-4-thiazolyl, 2-methyl-4-oxazolyl; or R1a, R1b together = trimethylene; R2 = Me, Et, Pr; X = 2-pyridyl, 2-methyl-4-thiazolyl, 2-methyl-4-oxazolyl; or simultaneously R1a = R1b = Me; R2 = Me, Et, Pr; X = 2-pyridyl, 2-methyl-4-thiazolyl or 2-methyl-4-oxazolyl; and the N and/or S atoms in X can be in an oxidized form; and if R2 and R8 = Me, X can only be a 2-pyridyl residue which is optionally oxidized at the nitrogen atom) and all possible stereoisomers and their mixts were prepared Thus II was prepared in a multistep sequence from the starting materials III and IV. The novel compds. interact with tubulin by stabilizing the formed microtubuli. The compds. are able to influence the cell division in a phase-specific manner and are suited for treating malignant tumors, for example, ovarian cancer, gastric carcinoma, colon cancer, breast cancer, lung cancer, head and neck cancer, malignant melanoma, and acute lymphocytic and myelocytic leukemia. The inventive compds. are suited for use in anti-angiogenic therapy as well as for treating chronic inflammatory diseases (psoriasis, arthritis). In order to prevent uncontrolled cell proliferations and to improve the compatibility of medical implants, the inventive compds. can be applied or incorporated in polymeric materials. The inventive compds. can be used alone or, in order to achieve additive or synergistic effects, in conjunction with addnl. constituents and substance classes which can be use in tumor therapy.

L102 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:332415 CAPLUS Full-text
TITLE: Epothilones.
AUTHOR(S): ***Klar, Ulrich; Skuballa, Werner; Schwede, Wolfgang; Buchmann, Bernd***
CORPORATE SOURCE: Preclinical Drug Research, Schering AG, Germany, Berlin, D-13342, Germany
SOURCE: Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), ORGN-288. American Chemical Society: Washington, D. C.
CODEN: 69CLAC
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB The new natural product class of epothilones seems to parallel the biol. behavior of paclitaxel regarding its action on the tubulin system although the chemical structures are quite different. Despite its impressive anti-proliferative effects also against multi drug resistant cell lines epothilone B shows severe toxicity at therapeutic relevant doses in vivo. Thus the need for epothilone analogs with improved properties is obvious. In contrast to paclitaxel structural modifications can be achieved more easily by total synthesis. Therefore we have developed a highly convergent total synthesis which allows an efficient preparation of large amts. of strategic important building blocks with high optical purity, high flexibility regarding structural modifications in most parts of the mol., efficient syntheses of analogs yielding sufficient amts. for in vivo characterization. Using this methodol., more than 250 analogs of epothilone B and D have been synthesized

```
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            MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
            SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ,
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            CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
    DE 19908763          A1    20000824    DE 1999-19908763        19990218
PRIORITY APPLN. INFO.:                     DE 1999-19908763    A   19990218
OTHER SOURCE(S):         MARPAT 133:193027
GI
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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Epothilone derivs. I (R1a, R1b = H, C1-C10-alkyl, aryl, C7-C20-aralkyl; (CH2)m m = 1-5; CH2OCH2; R2a, R2b = H, C1-C10-alkyl, aryl, C7-C20-aralkyl; (CH2)n n = 2-5; E = A or B where t = 1-2, w = 1-2; G, G1 = H, halogen, CN, R24, C1-C20-acyl, C1-C20-acyloxy, OR24, CO2R24, N3, NO2, NR24aR24b; R24a, R24b = R24, (CH2)e e = 4-6; R24 = R3a = H, C1-C10-alkyl, aryl, C7-C20-aralkyl; R14 = H, OR14a, halogen; R3b = OPG14; R3b, R4a = bond; R4a, R4b = H, F, C1-C10-alkyl, aryl, C7-C20-aralkyl; R5 = H, C1-C10-alkyl, aryl, C7-C20-aralkyl, (CH2)s-A where s = 1-4, A = OR22, halogen; R22 = H, protecting group; R6,R7 = H, bond, O; R8 = H, F C1-C10-alkyl, aryl, C7-C20-aralkyl; X = O, two alkoxy groups OR23, C2-C10-alkylene- α,ω-dihydroxy group straight or branched, H/OR9, CR10R11 where R23 = C1-C20-alkyl; R9 = H, protecting group; R10, R11 = H C1-C10-alkyl, aryl, C7-C20-aralkyl or together are a 5-7 membered carbocyclic ring; Y = O or 2 H atoms; Z = O, H/OR12 where R12 = O, protecting group) were prepared in addition to all possible stereoisomers and mixts. Thus II was prepared from 1,3-bis(hydroxymethyl)benzene in a multistep synthesis. These epothilone derivs. interact with tubulin by stabilizing the formed microtubule. The compds. are able to influence the cell division in a phase-specific manner and are suited for treating malignant tumors, for example, ovarian cancer, gastric carcinoma, colon cancer, breast cancer, lung cancer, head and neck cancer, malignant melanoma, and acute lymphocytic and myelocytic leukemia. These derivs. are suited for use in anti-angiogenic therapy as well as for treating chronic inflammatory diseases (psoriasis, arthritis). These compds. can be applied or incorporated in polymeric materials to prevent uncontrolled cell proliferations and to improve the compatibility of medical implants. They can be used alone or in conjunction with addnl. constituents and substance classes to achieve additive or synergistic effects in tumor therapy.

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L102 ANSWER 17 OF 24  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:         2000:592719  CAPLUS  Full-text
DOCUMENT NUMBER:          133:193025
TITLE:                    Preparation of new epothilone derivatives and their
                          pharmaceutical uses
INVENTOR(S):              Klar, Ulrich; Schwede, Wolfgang;
                          Skuballa, Werner; Buchmann, Bernd;
                          Schirner, Michael; Menrad, Andreas
PATENT ASSIGNEE(S):       Schering A.-G., Germany
SOURCE:                   PCT Int. Appl., 54 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
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LANGUAGE:                 German
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

    PATENT NO.          KIND   DATE        APPLICATION NO.          DATE
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    WO 2000049019        A2    20000824    WO 2000-EP1331           20000218
    WO 2000049019        A3    20010301
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            MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
            SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ,
            BY, KG, KZ, MD, RU, TJ, TM
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            DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
            CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
    DE 19908760          A1    20000824    DE 1999-19908760         19990218
PRIORITY APPLN. INFO.:                     DE 1999-19908760    A    19990218
OTHER SOURCE(S):         MARPAT 133:193025
GI
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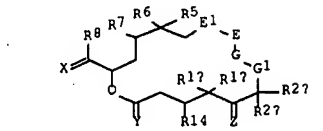

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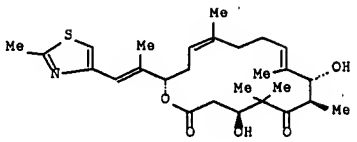

II

AB Epothilone derivs. I (R1a, R1b = H, C1-C10 alkyl, aryl; C7-C20 aralkyl; or together are (CH2)m m = 1-5; or CH2OCH2; R2a, R2b = H, C1-C10 alkyl, aryl; C7-C20 aralkyl; or together are (CH2)n n = 2-5; G1-G-E-E1 = CR3aR3b-CR4=CH-CH2; CR3aR3b-CD(T)R4-CHD(T)-CH2; (2,3-epoxy)-CR3aR3b-CR4OCH- CH2; CR3aR3b-COH(H)R4-CHOH(H)-CH2; CR3a=CR4-CH=CH where R3a = H, C1-C10 alkyl, aryl; C7-C20 aralkyl; R14 = H, OR14a, halogen, OSO2R14b; R3b = OPG14 or R3b, R14a = bond; R4 = H, C1-C10 alkyl, aryl; C7-C20 aralkyl; R5 = H, C1-C10 alkyl, aryl; C7-C20 aralkyl, (CH2)s-A s = 1-4, A = OR22 or halogen; R22 = H or protecting group; R6, R7 = H, O, bond; R8 = H, C1-C10 alkyl, aryl; C7-C20 aralkyl; X = O, OR23, C2-C10-alkylene-α,ω- dihydroxy which can be a straight chain or branched; H/OR9 or the group CR10R11 where R23 = C1-C20 alkyl; R9 = H or a protecting group; R10,R11 = H, C1-C20 alkyl, aryl; C7-C20 aralkyl or R10,R11 together form a 5-7 membered carbocyclic ring; Y = O or 2 H atoms; Z = O or H/OR12 where R12 = H or a protecting group) were prepared in addition to all possible stereoisomers and mixts. Thus II was prepared from (±)-1-acetoxypentan-4- one in a multistep synthesis. These epothilone derivs. interact with tubulin by

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000049021	A2	20000824	WO 2000-EP1333	20000218
WO 2000049021	A3	20001228		
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EP 1150980	A2	20011107	EP 2000-909205	20000218
EP 1150980	B1	20070822		
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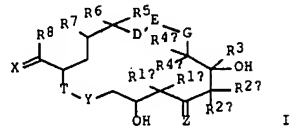
BR 2000008331	A	20020129	BR 2000-8331	20000218
HU 2001005478	A2	20020629	HU 2001-5478	20000218
JP 2002537301	T	20021105	JP 2000-599760	20000218
EE 200100431	A	20021216	EE 2001-431	20000218
NZ 513268	A	20040528	NZ 2000-513268	20000218
AT 370946	T	20070915	AT 2000-909205	20000218
IN 2001MN00940	A	20050304	IN 2001-MN940	20010806
BG 105802	A	20020329	BG 2001-105802	20010809
MX 2001PA08328	A	20020604	MX 2001-PA8328	20010816
NO 2001004013	A	20011018	NO 2001-4013	20010817
ZA 2001007648	A	20030107	ZA 2001-7648	20010917
US 6610736	B1	20030826	US 2001-913495	20011207
HK 1044945	A1	20051118	HK 2002-106485	20020903
US 2004014978	A1	20040122	US 2003-364337	20030212
US 6930102	B2	20050816		
US 2005187270	A1	20050825	US 2005-90841	20050325
PRIORITY APPLN. INFO.:			DE 1999-19908765 A	19990218
			DE 1999-19954230 A	19991104
			WO 2000-EP1333 W	20000218
			US 2001-913495 A3	20011207
			US 2003-364337 A3	20030212

OTHER SOURCE(S): MARPAT 133:193028
GI



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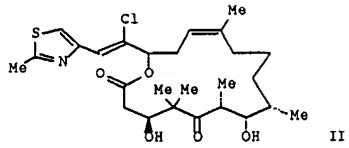


II

AB 16-Halogen epothilone derivs. I (R1a, R1b = R2a, R2b = H, C1-C10-alkyl, aryl, C7-C20-aralkyl, (CH2)m m = 2-5; R3 = H, C1-C10-alkyl, aryl, C7-C20-aralkyl; G = O, CH2; R4a, R4b = H, C1-C10-alkyl, aryl, C7-C20-aralkyl, (CH2)p p = 2-5; D-E = 1,2-ethanediyl, 1,2-ethenediyl, ethynyl, oxiranyl, 1,2-dihydroxy-1,2-ethanediyl, 1(2)-hydroxy-1,2- ethanediyl, CH2OH; R5 = H, C1-C10-alkyl, aryl, C7-C20-aralkyl, CO2H, CO2-alkyl, CH2OH, CH2O-alkyl, CH2O-acyl, CN, CH2NH2, CH2N(alkyl, acyl)1,2, CH2-halogen; R6, R7 = H, bond, O; R8 = halogen, CN; X = O, two alkoxy groups OR23, C2-C10-alkylene-α,ω-dihydroxy group straight or branched chain, H/OR9, CH10R11 where R23 = C1-C20-alkyl; R9 = H, or protecting group; R10, R11 = H, C1-C10-alkyl, aryl, C7-C20-aralkyl, 5-7 membered carbocyclic ring; T-Y = OC(=O), OCH2, CH2C(=O), NR24C(=O), NR24SO2; R24 = H, C1-C10-alkyl; Z = O, H/OR12 where R12 = H or protecting group) were prepared in addition to all possible stereoisomers and mixts. Thus II was prepared from 2-methyl-4-thiazolecarboxaldehyde in a multistep synthesis. The IC50 of II was 5.1 nM on MCF-7 breast tumor and had an IC50 of 37 nM on the multidrug resistant carcinoma NCI/ADR.

L102 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:592720 CAPLUS Full-text
DOCUMENT NUMBER: 133:193027
TITLE: Preparation of new epothilone derivatives having pharmaceutical application as antitumor agents
INVENTOR(S): ***Klar, Ulrich; Schwede, Wolfgang; Buchmann, Bernd; Skuballa, Werner;*** Schirner, Michael; Grimm, Michael
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000049020	A2	20000824	WO 2000-EP1332	20000218
WO 2000049020	A3	20001228		

IN 2001MN01305	A	20070504	IN 2001-MN1305		20011019
BG 106053	A	20020531	BG 2001-106053		20011026
NO 2001005278	A	20011221	NO 2001-5278		20011029
MX 2001PA11039	A	20030630	MX 2001-PA11039		20011030
ZA 2001009859	A	20030228	ZA 2001-9859		20011129
US 7125893	B1	20061024	US 2002-979939		20020606
US 2005113429	A1	20050526	US 2004-965802		20041018
IN 2005MN00837	A	20070608	IN 2005-MN837		20050802
US 2006046997	A1	20060302	US 2005-214988		20050831
JP 2007224038	A	20070906	JP 2007-104224		20070411
PRIORITY APPLN. INFO.:			DE 1999-19921086	A	19990430
			DE 1999-19954228	A	19991104
			DE 2000-10013363	A	20000309
			DE 2000-10015836	A	20000327
			JP 2000-615619	A3	20000501
			WO 2000-IB657	W	20000501
			IN 2001-MN1305	A3	20011019
			US 2002-979939	A3	20020606

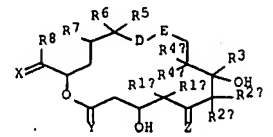
OTHER SOURCE(S): MARPAT 133:321769

AB The title compds. were prepared by various combinations of 3 fragments making up the mols. Thus, [4S,7R,8S,9S,13Z,16S(E)]-4,8-dihydroxy-16-[1- methyl-2-(2-pyridyl)ethenyl]-1-oxa-5,5,9,13-tetramethyl-7-(3-butynyl)-13- cyclohexadecene-2,6-dione was prepared in several steps starting from (4S)-4-(2-methyl-1-oxo-2-propyl)-2,2-dimethyl[1,3]dioxane and 5-(trimethylsilyl)-4-pentynylmagnesium bromide.

L102 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:738730 CAPLUS Full-text
DOCUMENT NUMBER: 133:309795
TITLE: Preparation of new epothilone derivatives and their pharmaceutical uses
INVENTOR(S): ***Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd;*** Schirner, Michael
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 74 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19908767	A1	20001019	DE 1999-19908767	19990218
PRIORITY APPLN. INFO.:			DE 1999-19908767	19990218

OTHER SOURCE(S): MARPAT 133:309795
GI



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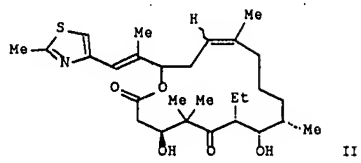

II

AB New epothilone derivs. I (R1a,R1b = R2a,R2b = same or different H, alkyl, aryl, aralkyl or (CH2)m,n m, n = 2-5; R3 = H, alkyl, aryl, aralkyl; R4a,R4b = same or different H, alkyl, aryl, aralkyl or (CH2)p = 2-5, CH2CH2, CH=CH, C.tplbond.C, epoxy, CH(OH)CH(OH), CH(OH)CH2; D-E = a group; R5 = H, alkyl, aryl, aralkyl; R6,R7 = H, bond, O; R8 = H, alkyl, aryl, aralkyl; X = O, OR23 alkylene-α,-ω-dioxy group straight or branched, OR9 or the CR10R11 group where R23 = alkyl, R9 = H or protecting group and R10,R11 = same or different H, alkyl, aryl, aralkyl or R10,R11 = together with methylene are a 5-7 membered carbocyclic ring; Y = O or two H; Z = O or H/OR12 and R12 = H or a protecting group) were prepared Thus E- and Z-II were prepared via a multistep synthesis. I cooperate with tubulin by stabilizing formed microtubuli. I are able phase specifically to affect the cell division and are suitable for the treatment of malignant ovarian, stomach, colon, adeno, breast, lung, head and neck tumors, malignant melanomas, acute lymphocytic and myelocytic leukemia. Derivs. of I are suitable for use in anti-angiogenic therapy as well as for treating chronic inflammatory diseases (psoriasis, arthritis). In order to prevent uncontrolled cell proliferations and to improve the compatibility of medical implants I can be applied or incorporated into polymeric materials. I can be used alone or to achieve additive or synergistic effects in combination with further principles and substance classes applicable in tumor therapy.

L102 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:592721 CAPLUS Full-text
DOCUMENT NUMBER: 133:193028
TITLE: Preparation of 16-halogen epothilone derivatives and their use as antitumor agents
INVENTOR(S): ***Klar, Ulrich; Skuballa, Werner; Buchmann, Bernd; Schwede, Wolfgang;*** Schirner, Michael
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066589	A1	20001109	WO 2000-IB657	20000501
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19921086	A1	20001102	DE 1999-19921086	19990430
DE 19954228	A1	20010913	DE 1999-19954228	19991104
DE 10015836	A1	20011011	DE 2000-10015836	20000327
CA 2371226	A1	20001109	CA 2000-2371226	20000501
BR 2000010190	A	20020108	BR 2000-10190	20000501
EP 1173441	A1	20020123	EP 2000-922826	20000501
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002543203	T	20021217	JP 2000-615619	20000501
EE 200100568	A	20030217	EE 2001-568	20000501
NZ 514989	A	20040227	NZ 2000-514989	20000501
AU 772750	B2	20040506	AU 2000-43103	20000501
IN 2001MN01305	A	20070504	IN 2001-MN1305	20011019
BG 106053	A	20020531	BG 2001-106053	20011026
NO 2001005278	A	20011221	NO 2001-5278	20011029
MX 2001PA11039	A	20030630	MX 2001-PA11039	20011030
US 7125893	B1	20061024	US 2002-979939	20020606
IN 2005MN00837	A	20070608	IN 2005-MN837	20050802
US 2006046997	A1	20060302	US 2005-214988	20050831

PRIORITY APPLN. INFO.:	DE 1999-19921086	A1	19990430
	DE 1999-19954228	A1	19991104
	DE 2000-10015836	A1	20000327
	DE 2000-10013363	A	20000309
	WO 2000-IB657	W	20000501
	IN 2001-MN1305	A3	20011019
	US 2002-979939	A3	20020606

OTHER SOURCE(S): MARPAT 133:362656
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The antitumor agents, 6-alkenyl-, 6-alkynyl- and 6-epoxyepothilones I (R1a, R1b are same or different = H, C1-C10 alkyl, C6-C12 aryl, C7-C20 aralkyl each optionally substituted; or together = (CH2)m m = 1-5 or -CH2OCH2-; R2a(R2b replace a with b) = H, substituted alkyl, aryl, aralkyl, -(CH2)ra-C.tplbond.(or =)C-(CH2)pa-R26a, Q, Q1 where n = 0-5; ra, rb = the same or different and = 0-4; pa, pb = the same or different and = 0-3; R3a = H, substituted alkyl, aryl or aralkyl; R3b = OH, OPG14; R14 = H, OR14a, halogen and R14a = H, SO2-alkyl, SO2-aryl or SO2-aralkyl; R4 = H, substituted alkyl, aryl or aralkyl, halogen, OR25, CN; R26a, R26b = same or different = H, substituted alkyl, aryl or aralkyl, C1-C10 acyl or if pa or pb > 0, addnl. a group OR27; R25 = R27 = R22 = H, PG; R5 = H, substituted alkyl, aryl or aralkyl, (CH2)sT s = 1-4, T = OR22 or halogen; R6, R7 = H or together = bond or O; G = X=CR8 or bi- or tricyclic

aryl radical and R8 = H, halogen, CN, or substituted alkyl, aryl or aralkyl; X = O, two OR23 groups, C2-C10-alkylene-α,ω-dioxy straight chain or branched; H/OR9 or CR10R11 group and R23 = alkyl radical, R9 = H, PG, R10,R11 = same or different = H, substituted alkyl, aryl or aralkyl, or together with the methylene are a 5-7 carbocyclic ring; D-E = CH2CH2 or OCH2; A = OC(O), OCH2, CH2C(O), NR29C(O), NR29SO2 and R29 = H, alkyl; Z = O or H/OR12 and R12 = H, PG) were prepared Thus II was prepared in a multistep synthesis starting from (4S)-4-(2-methyl-1-oxoprop-2-yl)-2,2- dimethyl[1,3]dioxane and 5-trimethylsilylpent-4-in-1-yl magnesium bromide. II had an IC50 value [nM] of 3.0 for the growth inhibition of human MCF-7 breast- and 75 for multidrug resistant NCI/ADR carcinoma cell lines with a selectivity of 2.5. The new epothilone derivs. interact with tubulin by stabilizing microtubuli that are formed. They are able to influence the cell-splitting in a phase-specific manner and are therefore useful in treating diseases or conditions associated with the need for cell growth, division and/or proliferation. Thus the epothilone derivs. are suitable for treating malignant tumors, e.g., ovarian, stomach, colon, adeno-, breast, lung, head and neck carcinomas, malignant melanoma, acute lymphocytic and myelocytic leukemia; and for anti-angiogenesis therapy as well as for treatment of chronic inflammatory diseases (such as psoriasis, arthritis).

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L102 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2000:772379 CAPLUS Full-text
DOCUMENT NUMBER:	133:321769
TITLE:	6-Alkenyl and 6-alkynyl derivatives of epothilone
INVENTOR(S):	***Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd;*** Hoffmann, Jens; Lichtner, Rosemarie
PATENT ASSIGNEE(S):	Schering A.-G., Germany
SOURCE:	Ger. Offen., 18 pp. CODEN: GWXXBX
DOCUMENT TYPE:	Patent
LANGUAGE:	German
FAMILY ACC. NUM. COUNT:	3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19921086	A1	20001102	DE 1999-19921086	19990430
CA 2371226	A1	20001109	CA 2000-2371226	20000501
WO 2000066589	A1	20001109	WO 2000-IB657	20000501
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000010190	A	20020108	BR 2000-10190	20000501
EP 1173441	A1	20020123	EP 2000-922826	20000501
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, LT, LV, FI, RO				
HU 200201010	A2	20020828	HU 2002-1010	20000501
JP 2002543203	T	20021217	JP 2000-615619	20000501
EE 200100568	A	20030217	EE 2001-568	20000501
NZ 514989	A	20040227	NZ 2000-514989	20000501
AU 772750	B2	20040506	AU 2000-43103	20000501

TITLE: Subcellular distribution of epothilones in human tumor cells
AUTHOR(S): Lichtner, R. B.; Rotgeri, A.; Bunte, T.; ***Buchmann, B.***; Hoffmann, J.; ***Schwede, W.***; ***Skuballa, W.***; ***Klar, U.***
CORPORATE SOURCE: Research Laboratories of Schering AG, Berlin, 13342, Germany
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2001), 98(20), 11743-11748
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Epothilones are a new class of natural and potent antineoplastic agents that stabilize microtubules. Although 12,13-epoxide derivs. are potent antiproliferative agents, the activities of the corresponding 12,13-olefin analogs are significantly decreased. These data were confirmed for two new analogs, 6-propyl-EpoB (pEB) and 6-propyl-EpoD (pED), in comparison with the natural compds. EpoB/EpoD, by using human A431, MCF7, and MDR1-overexpressing NCl/Adr cells. By using tritiated pEB/pED, compound uptake, release, and nuclear accumulation were investigated in A431 and NCl/Adr cells. In these cells, epothilones can principally be recognized and exported by verapamil-sensitive efflux pumps, which are not identical to MDR1. The degree of export depends on the structure, olefin vs. epoxide-analog, and also on the intracellular drug concentration The accumulation of pED used at 3.5 or 70 nM, resp., was increased in the presence of 10 μM Verapamil in both cell lines 2- to 8-fold. In contrast, the intracellular levels of pEB were affected by Verapamil only at 3.5 nM pEB in NCl/Adr (2-fold) and not in A431 cells. In addition, strong nuclear accumulation was observed for pEB (40-50%) but not paclitaxel or pED (5-15%) in both cell lines. Our study suggests that differences in growth inhibitory efficacy between epoxide and olefin analogs may be based on different mechanisms of drug accumulation and subcellular distribution.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L102 ANSWER 11 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:676638 CAPLUS Full-text
DOCUMENT NUMBER: 135:236394
TITLE: Synthesis of radioactively labeled epothilone derivatives and their biochemical and pharmaceutical usage
INVENTOR(S): ***Klar, Ulrich***; Gay, Juergen; ***Skuballa, Werner***; ***Schwede, Wolfgang***; ***Buchmann, Bernd***; Bunte, Thomas; Lichtner, Rosemarie
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001066154	A2	20010913	WO 2001-EP2699	20010309

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,

LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: DE 2000-10013363 A 20000309
OTHER SOURCE(S): MARPAT 135:236394
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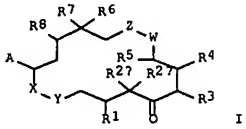
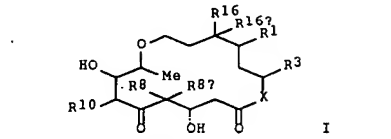


I

AB The invention relates to novel radioactively labeled pharmacol. effective epothilone derivs. of general formula (I), where R1 represents O-PG and hydroxyl, where PG is a protective group; R2a, R2b are the same or different and represent, independent of one another, hydrogen C1-C10 alkyl, aryl, C7-C20 aralkyl or, together, represent a (CH2)m group, where m is equal to 1, 2, 3, 4 or 5; R3 represents a C2-C10 alkyl group, a C2-C10 alkenyl group or a C8-C20 aralkyl each containing 2n tritium atoms, where n equals 1 or 2; R4 represents O-PG and hydroxyl; R5 represents hydrogen C1-C10 alkyl, aryl, C7-C20 aralkyl and halogen; W-Z represents a CH2-CH2, CH2-O or O-CH2 group; R6 represents hydrogen, C1-C10 alkyl, aryl, C7-C20 aralkyl, (CH2)s-V and halogen, where s equals 1, 2, 3 or 4 and V represents O-PG, hydroxyl or halogen; R7, R8 each represent a hydrogen atom and, together, represent an addnl. bond or an oxygen atom; A represents aryl, C7-C20 aralkyl, and a group R10-CH=C9-, where R9 represents hydrogen, halogen, CN, C1-C20 alkyl, aryl, and C7-C20 aralkyl, and R10 represents hydrogen, C1-C20 alkyl-, aryl-, C7-C20 aralkyl, and; X-Y represents an O-C(=O), an O-CH2, a CH2-C(=O), an NR11-C(=O) and an NR11-SO2 group, wherein R11 represents hydrogen and C1-C10 alkyl. The novel compds. of formula I are valuable pharmaceuticals and valuable diagnostic probes for elucidating, for example, active mechanisms and biochem., pharmacokinetic and/or pharmacodynamic processes.

L102 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:790507 CAPLUS Full-text
DOCUMENT NUMBER: 133:362656
TITLE: Preparation of 6-alkenyl-, 6-alkynyl- and 6-epoxyepothilone derivatives and their antitumor activity
INVENTOR(S): ***Klar, Ulrich***; ***Schwede, Wolfgang***; ***Skuballa, Werner***; ***Buchmann, Bernd***; Hoffmann, Jens; Lichtner, Rosemarie
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 298 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English



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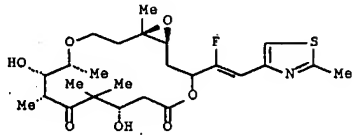


II

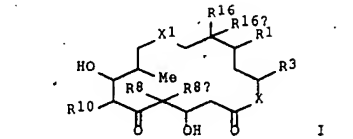
AB Oxa-epothilones, such as I [R3 = heteroaryl, heteroarylalkenyl, heteroarylhaloalkenyl,etc.; R8, R8a = H, alkyl, arylalkyl; R8R8a = alkylene, heteroalkene; R10 = H, alkyl, alkenyl, alkynyl; R1R16a = bond, O; R16 = H, CN, alkyl, halogen; X = O, NH], were prepared for a variety of therapeutic uses, such as treatment of malignant tumors, proliferative diseases, leukemia, and chronic inflammatory diseases, as well as for anti-angiogenic SE therapy. Thus, oxa-epothilone II was prepared via a multistep synthetic sequence starting from (R)-1,2-propanediol, and [(3S,4Z)-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-fluoro-5-(2-methyl-4-thiazolyl)-4-pentenyl]triphenylphosphonium iodide,. Pharmaceutical formulations of the prepared oxa-epothilones were discussed, but specific biol. activity data was not presented.

L102 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:780370 CAPLUS Full-text
DOCUMENT NUMBER: 135:331294
TITLE: Preparation of epothilone derivatives for pharmaceutical use in the treatment of cancer
INVENTOR(S): ***Buchmann, Bernd; Klar, Ulrich; Skuballa, Werner; Schwede, Wolfgang***; Hoffmann, Jens; Lichtner, Rosemarie
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 42 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10020517	A1	20011025	DE 2000-10020517	20000419
WO 2001081342	A2	20011101	WO 2001-EP4552	20010419

WO 2001081342	A3	20020510			
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1276740	A2	20030122	EP 2001-936262		20010419
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003531207	T	20031021	JP 2001-578432		20010419
NO 2002005029	A	20021018	NO 2002-5029		20021018
US 2004058969	A1	20040325	US 2002-257925		20021018
PRIORITY APPLN. INFO.:			DE 2000-10020517	A	20000419
			WO 2001-EP4552	W	20010419

OTHER SOURCE(S): MARPAT 135:331294
GI



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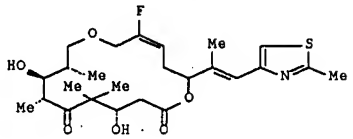


II

AB Epothilones, such as I [R3 = heteroaryl, heteroarylalkenyl, heteroarylhaloalkenyl,etc.; R8, R8a = H, alkyl, arylalkyl; R8R8a = alkylene, heteroalkene; R10 = H, alkyl, alkenyl, alkynyl; R1R16a = bond, O; R16 = H, CN, alkyl, halogen; X = O, NH; X1 = O, CH2], were prepared for a variety of therapeutic uses, such as treatment of malignant tumors, proliferative diseases, leukemia, and chronic inflammatory diseases. Thus, epothilone II was prepared via a multistep synthetic sequence starting from (3S)-dihydro-3-hydroxy-4,4-dimethyl-2(3H)-furanone, L-(-)-malic acid, and [(2-methyl-4-thiazolyl)methyl]phosphonic acid di-Et ester. Pharmaceutical formulations of the prepared oxa-epothilones were discussed, but specific biol. activity data was not presented.

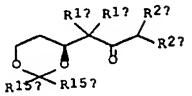
L102 ANSWER 10 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:729040 CAPLUS Full-text
DOCUMENT NUMBER: 136:95676

Bernd; Schwede, Wolfgang; Skuballa, Werner
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003053949	A1	20030703	WO 2002-EP14758	20021223
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10164592	A1	20030703	DE 2001-10164592	20011221
AU 2002356783	A1	20030709	AU 2002-356783	20021223
US 2003176710	A1	20030918	US 2002-326263	20021223

PRIORITY APPLN. INFO.: DE 2001-10164592 A 20011221
WO 2002-EP14758 W 20021223

OTHER SOURCE(S): CASREACT 139:85166; MARPAT 139:85166
GI



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AB The invention relates to C1-C6 fragments I [R1a, R1b = H, C1-10-alkyl, aryl, C7-20-aralkyl, (CH2)m; m = 2 - 5; R2a, R2b = H, C1-10-alkyl, C1-10-alkenyl, C1-10-alkynyl, C7-20-aralkyl, (CH2)n; n = 2 - 5; R15a, R15b = H, C1-10-alkyl, aryl, C7-20-aralkyl, (CH2)q; q = 3 - 6] of epothilones and to an efficient method for producing such fragments and the derivs. thereof. Thus, (4S)-4-(2-methyl-3-oxohept-6-en-2-yl)-2,2-dimethyl-1,3- dioxane [I; R1a = R1b = Me, R2a = CH2CH:CH2, R2b = H, R15a = R15b =Me] was prepared from (3S)-1-hydroxy-2,2-dimethyl-3-(tetrahydropyranyloxy)-4- pentene, (S)-HOCH2CMe2CH(OTHP)CH:CH2, via O-benzylation with PhCH2Br, hydroboration with BH3-THF complex, dehydrotetrahydropyranylation- isopropylidenation with Me2C(OMe)2 in MeCOMe containing catalytic tosyl acid, hydrogenolytic debenzylation, Swern oxidation, Grignard reaction with MeMgBr, oxidn, with TPAT in CH2Cl2 contg, NOmethylmorpholine N-oxide and alkylation with allyl bromide.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L102 ANSWER 7 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:132142 CAPLUS Full-text
DOCUMENT NUMBER: 136:309773
TITLE: Synthesis and biological activity of epothilones
AUTHOR(S): ***Klar, Ulrich; Skuballa, Werner; Buchmann, Bernd; Schwede, Wolfgang;*** Bunte, Thomas; Hoffmann, Jens; Lichtner, Rosemarie B.
CORPORATE SOURCE: Research Laboratories of Schering AG, Berlin, D-13342, Germany
SOURCE: ACS Symposium Series (2001), 796(Anticancer Agents), 131-147
CODEN: ACSMC8; ISSN: 0097-6156
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. The total synthesis and biol. activity of epothilone analogs are described. Selected SAR data indicate the possibility to improve activity and selectivity by structural modifications. The new compds. may help to elucidate the therapeutic potential of this class of anticancer drugs.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L102 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:780372 CAPLUS Full-text
DOCUMENT NUMBER: 135:331295
TITLE: Preparation of oxa-epothilone derivatives for pharmaceutical use in the treatment of cancer
INVENTOR(S): ***Schwede, Wolfgang; Klar, Ulrich; Skuballa, Werner; Buchmann, Bernd;*** Hoffmann, Jens; Lichtner, Rosemarie
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 46 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10020899	A1	20011025	DE 2000-10020899	20000420
WO 2001081341	A2	20011101	WO 2001-EP4551	20010419
WO 2001081341	A3	20020425		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AE				

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THE REST OF THIS BIB INFORMATION WAS NOT AVAILABLE AT THE TIME OF PRINTING

active ingredients II [AK = OC(:O), OCH2, CH2C(:O), NR29C(:O), NR29SO2; R29 = H, C1-6-alkyl] according to known methods. The invention also relates to the corresponding C1-C12 fragments.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L102 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:719306 CAPLUS Full-text
DOCUMENT NUMBER: 139:240340
TITLE: Use of epothilones in the treatment of brain diseases associated with proliferative processes
INVENTOR(S): Lichtner, Rosemarie; Rotgeri, Andrea; ***Klar, Ulrich***; Hoffmann, Jens; ***Buchmann, Bernd***; ***Schwede, Wolfgang***; ***Skuballa, Werner***
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003074053	A1	20030912	WO 2003-EP2085	20030228
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1340498	A1	20030903	EP 2002-4745	20020301
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CA 2477403	A1	20030912	CA 2003-2477403	20030228
AU 2003215618	A1	20030916	AU 2003-215618	20030228
EP 1480643	A1	20041201	EP 2003-743360	20030228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003008154	A	20050104	BR 2003-8154	20030228
JP 2005525360	T	20050825	JP 2003-572570	20030228
MX 2004PA08450	A	20050713	MX 2004-PA8450	20040901
NO 2004004175	A	20041201	NO 2004-4175	20040930
PRIORITY APPLN. INFO.:			EP 2002-4745	A 20020301
			US 2002-361062P	P 20020301
			WO 2003-EP2085	W 20030228

OTHER SOURCE(S): MARPAT 139:240340
AB The invention provides the use of an Epothilone, which shows an average distribution coefficient between plasma and brain of 0.3 to 1.5 in the mouse i.v. bolus injection assay, for the preparation of a medicament for the treatment of a brain disease associated with proliferative processes.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L102 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2003:693140 CAPLUS Full-text
DOCUMENT NUMBER: 139:191465
TITLE: Use of epothilones in the treatment of brain diseases associated with proliferative processes
INVENTOR(S): Lichtner, Rosemarie; Rotgeri, Andrea; ***Buchmann, Bernd***; Hoffmann, Karin; ***Klar, Ulrich***; ***Schwede, Wolfgang***; ***Skuballa, Werner***
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: Eur. Pat. Appl., 27 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1340498	A1	20030903	EP 2002-4745	20020301
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
CA 2477403	A1	20030912	CA 2003-2477403	20030228
WO 2003074053	A1	20030912	WO 2003-EP2085	20030228
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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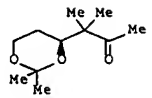
AU 2003215618	A1	20030916	AU 2003-215618	20030228
US 2004019088	A1	20040129	US 2003-375043	20030228
EP 1480643	A1	20041201	EP 2003-743360	20030228
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003008154	A	20050104	BR 2003-8154	20030228
CN 1649587	A	20050803	CN 2003-809761	20030228
JP 2005525360	T	20050825	JP 2003-572570	20030228
MX 2004PA08450	A	20050713	MX 2004-PA8450	20040901
NO 2004004175	A	20041201	NO 2004-4175	20040930
ZA 2004007905	A	20060426	ZA 2004-7905	20040930
PRIORITY APPLN. INFO.:			EP 2002-4745	A 20020301
			US 2002-361062P	P 20020301
			WO 2003-EP2085	W 20030228

OTHER SOURCE(S): MARPAT 139:191465
AB The invention provides the use of an epothilone, which shows an average distribution coefficient between plasma and brain of 0.3-1.5 in the mouse i.v. bolus injection assay, for the preparation of a medicament for the treatment of a brain disease associated with proliferative processes.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L102 ANSWER 6 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:511314 CAPLUS Full-text
DOCUMENT NUMBER: 139:85166
TITLE: Method for producing C1-C6 fragments of epothilones and the derivatives thereof
INVENTOR(S): ***Klar, Ulrich***; Berger, Markus; ***Buchmann,***

DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:355075
GI



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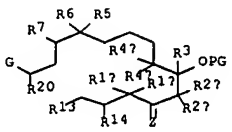
AB An efficient chiral pool synthesis of the C1-C6 fragment of epothilones, e.g. I, starting from readily available (-)-pantolactone is described.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L102 ANSWER 3 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:29293 CAPLUS Full-text
DOCUMENT NUMBER: 142:113814
TITLE: Method for producing C1-C15 fragments of epothilones and derivatives thereof
INVENTOR(S): ***Klar, Ulrich; Buchmann, Bernd; Schwede, Wolfgang; Skuballa, Werner***
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005003071	A1	20050113	WO 2004-EP6685	20040619
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10331004	A1	20050224	DE 2003-10331004	20030703
AU 2004254200	A1	20050113	AU 2004-254200	20040619
CA 2531078	A1	20050113	CA 2004-2531078	20040619
EP 1641734	A1	20060405	EP 2004-740122	20040619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
CN 1816514	A	20060809	CN 2004-80019005	20040619
BR 2004012179	A	20060822	BR 2004-12179	20040619
IN 2006DN00056	A	20070824	IN 2006-DN56	20060103
MX 2006PA00172	A	20060427	MX 2006-PA172	20060105

NO 2006000554	A	20060403	NO 2006-554		20060202
US 2007142675	A1	20070621	US 2006-563058		20060619
PRIORITY APPLN. INFO.:			DE 2003-10331004	A	20030703
			WO 2004-EP6685	W	20040619

OTHER SOURCE(S): CASREACT 142:113814; MARPAT 142:113814
GI



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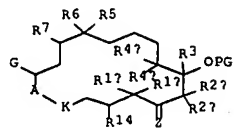

II

AB The invention relates to a method for preparing C1-C15 fragments I [R1a, R1b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R1aR1b = (CH2)m; m = 2 - 5; R2a, R2b = H, C1-10-alkyl, C2-10-alkenyl, C2-10-alkynyl, aryl, C7-20-aralkyl; R2aR2b = (CH2)n; n = 2 - 5; R3 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4a, R4b = = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4aR4b = (CH2)p; p = 2 - 5; R5 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R6, R7 = H; R6R7 = bond, O; G = X:CR8, bi- or tricyclic aryl; R8 = H, halogen, (un)substituted C1-20-alkyl, aryl, C7-20-aralkyl; X = O, (OR23)2, C2-10-alkylene- α,ω-dioxy, H(OR9), CR10R11; R23 = C1-20-alkyl; R9 = H, protecting group; R10, R11 = H, C1-10-alkyl, aryl, C7-20-aralkyl; CR10R11 = 5 - to 7-membered carbocycle; R13 = CH2OR13a, CH2-halo, CHO, CO2R13b, CO-halo; R13a, R14a = H, SO2alkyl, SO2-aryl, SO2-aralkyl; R13aR14a = (CH2)o, CR15aR15b; o = 2 - 4; R13b, R14b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R15a, R15b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R15aR15b = (CH2)q; q = 3 - 6; R20 = O-PG, NHR29, N3; Z = O, H(OR12); R12 = H, PG] of epothilones and derivs. The procedure comprises the bonding of a C1-C6 fragment, R13CH2CHR14CR1aR1bC(:O)CHR2aR2b, to a C7-C12 fragment, R5C(:V)(CH2)3CR4aR4bC(:W)R3a [V, W = O, (OR23)2, C2-10-alkylene- α,ω-dioxy, H(OR9)], to form a C1-C12 fragment, R5C(:V)(CH2)3CR4aR4bCR3a(O-PG14)CR2aR2bC(:Z)CR1aR1bCHR14CH2R13 [PG = H, protecting group], which is then treated with a C13-C15 fragment, G-CR20'CH2CHR7'R21 [R7' = H; R20' = halogen, N3, NHR29, OH, O-PG, NR29-PG, C1-20-(perfluoro)alkylsulfonyloxy, (C1-4-alkyl, NO2, Cl, Br-substituted) benzyloxy, NR29SO2Me, NR29C(:O)Me, CH2C(:O)Me; R21 = OH, halo, O-PG, P+Ph3Hal- (Hal = F, Cl, Br, I), P(O)(OQ)2 (Q = C1-10-alkyl, Ph), P(:O)Ph2; R29 = H, C1-6-alkyl], to form the C1-C15 epothilone intermediate product I. Thus, I [R1a = R1b = R5 = Me, R2a = CH2CH:CH2-β, R2b = R4b = H-α, R3 = H-β, R4a = Me-β, R6R7 = bond, R13 = CO2H, R14 = OSiMe2CMe3-β, R20 = OSiMe2CMe3-α, G = 2-methylbenzothiazol-5- yl, PG = SiMe2CMe3, Z = O] was prepared from (S)-4-(2-methyl-3-oxohept-6-en- 2-yl)-2,2-dimethyl-1,3-dioxane via lithiation and reaction with (2S,6RS)-2-methyl-6-[(tert-butyldimethylsilyl)oxy]heptanal, tetrahydropyranylation, desilylation with Bu4NF in THF, oxidation in CH2Cl2 containing N-methylmorpholine N-oxide and catalytic tetrapropylammonium perruthenate, Wittig reaction with [(3S)-3-(2-methylbenzothiazol-5- yl)propyl]triphenylphosphonium iodide, deisopropylidenation/detetrahydropy ranylation with catalytic 4-MeC6H4SO3H in EtOH, silylation with CF3SO2SiMe2CMe3, regioselective desilylation with (±)-camphor-10- sulfonic acid, Swern oxidation with DMSO/(COCl)2 in CH2Cl2 and carbonyl oxidation with NaOCl2 in aqueous THF/Me3COH. The produced C1-C15 epothilone intermediate products can be converted into the intrinsically

```
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DICTIONARY FILE UPDATES:  10 OCT 2007  HIGHEST RN 950149-06-1

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  Please note that search-term pricing does apply when
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REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
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FILE COVERS 1907 - 11 Oct 2007  VOL 147 ISS 16
FILE LAST UPDATED: 10 Oct 2007  (20071010/ED)

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'OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE

=> d stat que L100
L91          80 SEA FILE=CAPLUS ABB=ON  PLU=ON  KLAR U?/AU
L92         116 SEA FILE=CAPLUS ABB=ON  PLU=ON  BUCHMANN B?/AU
L93          60 SEA FILE=CAPLUS ABB=ON  PLU=ON  SCHWEDE W?/AU
L94         186 SEA FILE=CAPLUS ABB=ON  PLU=ON  SKUBALLA W?/AU
L102         24 SEA FILE=CAPLUS ABB=ON  PLU=ON  L91 AND L92 AND L93 AND L94
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=> => d ibib abs L102 tot

L102 ANSWER 1 OF 24  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2006:1337456  CAPLUS  Full-text
DOCUMENT NUMBER:         146:229070
TITLE:                   Total synthesis and antitumor activity of ZK-EPO: The
                         first fully synthetic epothilone in clinical
                         development
AUTHOR(S):               Klar, Ulrich; Buchmann, Bernd;
                         Schwede, Wolfgang; Skuballa, Werner;
                         Hoffmann, Jens; Lichtner, Rosemarie B.
CORPORATE SOURCE:        Schering AG, Research Center Eurpoe, Berlin, Germany
SOURCE:                  Angewandte Chemie, International Edition (2006),
                         45(47), 7942-7948
                         CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER:               Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE:           Journal
LANGUAGE:                English
OTHER SOURCE(S):         CASREACT 146:229070
GI
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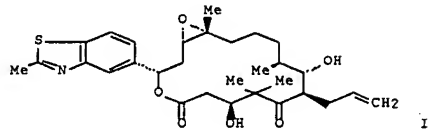

I

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AB    From about 350 active epothilone analogs synthesized by a highly convergent
      synthesis, ZK-EPO (I) was chosen for clin. development on the basis of its
      outstanding preclin. data.  This compound exhibits higher activity and
      efficacy than taxanes, such as paclitaxel and second-generation epothilones, a
      fast and efficient cellular uptake, no recognition by efflux mechanisms, and
      an improved therapeutic window.
REFERENCE COUNT:         39    THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L102 ANSWER 2 OF 24  CAPLUS  COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:        2005:132732  CAPLUS  Full-text
DOCUMENT NUMBER:         142:355075
TITLE:                   Efficient chiral pool synthesis of the C1-C6 fragment
                         of epothilones
AUTHOR(S):               Klar, Ulrich; Roehr, Bodo; Kuczynski, Frank;
                         Schwede, Wolfgang; Berger, Markus;
                         Skuballa, Werner; Buchmann, Bernd
CORPORATE SOURCE:        Research Laboratories of Schering AG, Berlin, 13342,
                         Germany
SOURCE:                  Synthesis (2005), (2), 301-305
                         CODEN: SYNTBF; ISSN: 0039-7881
PUBLISHER:               Georg Thieme Verlag
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             D STAT QUE L19

FILE 'BABS' ENTERED AT 15:47:02 ON 11 OCT 2007
             D STAT QUE L14

FILE 'ZCAPLUS, BEILSTEIN, BABS' ENTERED AT 15:47:21 ON 11 OCT 2007
L25          25 DUP REM L6 L19 L14 (7 DUPLICATES REMOVED)
                   ANSWERS '1-18' FROM FILE ZCAPLUS
                   ANSWERS '19-25' FROM FILE BEILSTEIN
             D IBIB ABS HITSTR L25 1-18
             D IDE ALLREF L25 19-25

FILE HOME

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Oct  5, 2007 (20071005/UP).

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES:   10 OCT 2007  HIGHEST RN 950149-06-1
DICTIONARY FILE UPDATES:  10 OCT 2007  HIGHEST RN 950149-06-1

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TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

  Please note that search-term pricing does apply when
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predicted properties as well as tags indicating availability of
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on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

FILE ZCAPLUS

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FILE LAST UPDATED: 10 Oct 2007  (20071010/ED)

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  This file contains CAS Registry Numbers for easy and accurate
  substance identification.
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=>  d his full

     (FILE 'HOME' ENTERED AT 15:09:07 ON 11 OCT 2007)

     FILE 'STNGUIDE' ENTERED AT 15:22:34 ON 11 OCT 2007

     FILE 'REGISTRY' ENTERED AT 15:31:01 ON 11 OCT 2007
L1             STRUCTURE UPLOADED
L2           0 SEA SSS SAM L1
L3             SCREEN 1008
L4           0 SEA SSS SAM L1 AND L3
L5          68 SEA SSS FUL L1 AND L3
             SAVE TEMP LAO058STR1CL/A L5

     FILE 'ZCAPLUS' ENTERED AT 15:37:30 ON 11 OCT 2007
L6          18 SEA ABB=ON  PLU=ON  L5
             E US2006-563058/APPS
L7           1 SEA ABB=ON  PLU=ON  US2006-563058/AP
             D SCA
L8           1 SEA ABB=ON  PLU=ON  L6 AND L7
             D SCA

     FILE 'BEILSTEIN' ENTERED AT 15:40:57 ON 11 OCT 2007
L9           0 SEA SSS SAM L1
L10          0 SEA SSS SAM L1 AND L3
L11         38 SEA SSS FUL L1 AND L3
L12         26 SEA ABB=ON  PLU=ON  L11/COM
L13          5 SEA ABB=ON  PLU=ON  L12 AND BABSAN/FA
             SEL BABSAN

     FILE 'BABS' ENTERED AT 15:42:39 ON 11 OCT 2007
L14          7 SEA ABB=ON  PLU=ON  (6300090/BABSAN OR 6630563/BABSAN OR
             6085475/BABSAN OR 6376421/BABSAN OR 6410256/BABSAN OR 6473119/B
             ABSAN OR 6597156/BABSAN)

     FILE 'BEILSTEIN' ENTERED AT 15:43:07 ON 11 OCT 2007
L15         21 SEA ABB=ON  PLU=ON  L12 NOT L13
L16         14 SEA ABB=ON  PLU=ON  L15 AND RN/FA

     FILE 'REGISTRY' ENTERED AT 15:43:45 ON 11 OCT 2007
L17         14 SEA ABB=ON  PLU=ON  L5 AND BEILSTEIN/LC NOT CAPLUS
L18          0 SEA ABB=ON  PLU=ON  L5 AND BEILSTEIN/LC NOT CAPLUS/LC

     FILE 'BEILSTEIN' ENTERED AT 15:44:11 ON 11 OCT 2007
L19          7 SEA ABB=ON  PLU=ON  L15 NOT L16
L20        252 SEA ABB=ON  PLU=ON  KLAR U?/AU
L21        351 SEA ABB=ON  PLU=ON  BUCHMANN B?/AU
L22        436 SEA ABB=ON  PLU=ON  SCHWEDE W?/AU
L23        369 SEA ABB=ON  PLU=ON  SKUBALLA W?/AU
L24          0 SEA ABB=ON  PLU=ON  L19 AND (L20 OR L21 OR L22 OR L23)
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     FILE 'REGISTRY' ENTERED AT 15:46:28 ON 11 OCT 2007

     FILE 'ZCAPLUS' ENTERED AT 15:46:31 ON 11 OCT 2007
             D STAT QUE L6

     FILE 'BEILSTEIN' ENTERED AT 15:46:51 ON 11 OCT 2007
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Field Availability:

Code	Name	Occurrence
BRN	Beilstein Records	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	3
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
DED	Entry Date	1
DUPD	Update Date	1
NMR	Nuclear Magnetic Resonance	1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
RX	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

All References:
ALLREF

1. Aberhart et al., J.Chem.Soc.Perkin Trans.1, CODEN: JCPRB4, <1974>, 816,823

BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	6
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
DED	Entry Date	1
DUPD	Update Date	1
CDER	Chemical Derivative	1

This substance also occurs in Reaction Documents:

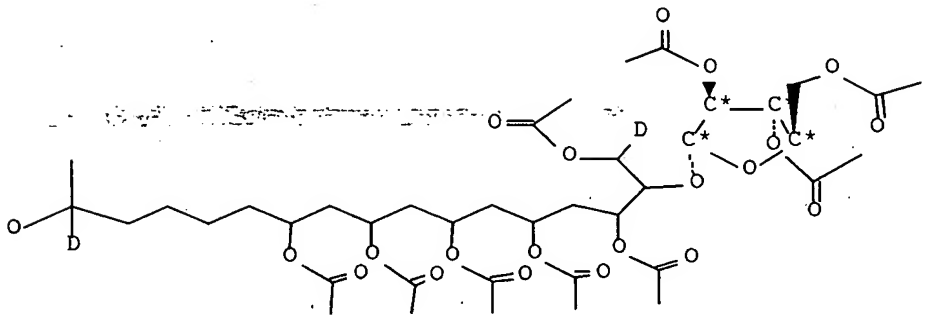
Code	Name	Occurrence
RX	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

All References:
ALLREF

1. Fehr,T. et al., J.Chem.Soc.Perkin Trans.1, CODEN: JCPRB4, <1974>, 836-847

L25 ANSWER 25 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN):	1677640
Molec. Formula (MF):	C40 H60 D2 O21
Molecular Weight (MW):	880.93
Lawson Number (LN):	17586, 1155, 680
File Segment (FS):	Stereo compound
Compound Type (CTYPE):	heterocyclic
Constitution ID (CONSID):	1560573
Tautomer ID (TAUTID):	1638549
Beilstein Citation (BSO):	5-17
Entry Date (DED):	1988/11/30
Update Date (DUPD):	1990/02/07



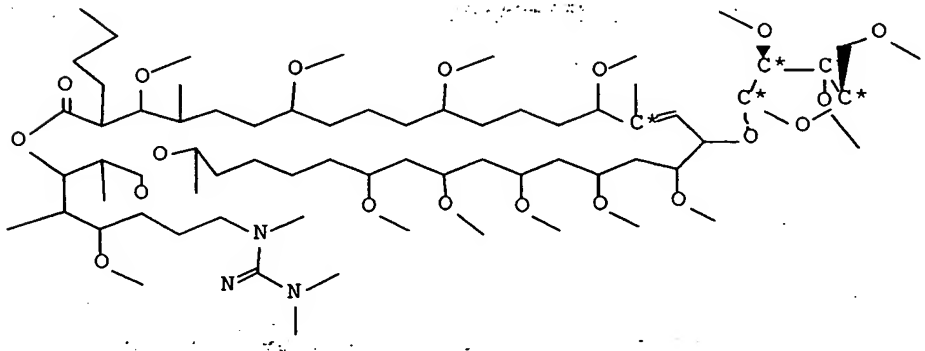
RX	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

All References:
ALLREF

1. Aberhart et al., J.Chem.Soc.Perkin Trans.1, CODEN: JCPRB4, <1974>, 816,823

L25 ANSWER 24 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN):	1677845
Chemical Name (CN):	2-butyl-18-(3,4-dimethoxy-5-methoxymethyl-tetrahydro-furan-2-yloxy)-32-hydroxy-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-tritriacont-16-enoic acid 1-(2-hydroxy-1-methyl-ethyl)-3-methoxy-2-methyl-6-(N,N',N'-trimethyl-guanidino)-hexyl ester
Autonom Name (AUN):	2-butyl-18-(3,4-dimethoxy-5-methoxymethyl-tetrahydro-furan-2-yloxy)-32-hydroxy-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-tritriacont-16-enoic acid 1-(2-hydroxy-1-methyl-ethyl)-3-methoxy-2-methyl-6-(N,N',N'-trimethyl-guanidino)-hexyl ester
Molec. Formula (MF):	C71 H139 N3 O19
Molecular Weight (MW):	1338.89
Lawson Number (LN):	17586, 3238, 2817, 2294, 1762, 289
File Segment (FS):	Stereo compound
Compound Type (CTYPE):	heterocyclic
Constitution ID (CONSID):	1561576
Tautomer ID (TAUTID):	1636624
Beilstein Citation (BSO):	5-17
Entry Date (DED):	1988/11/30
Update Date (DUPD):	1991/03/25



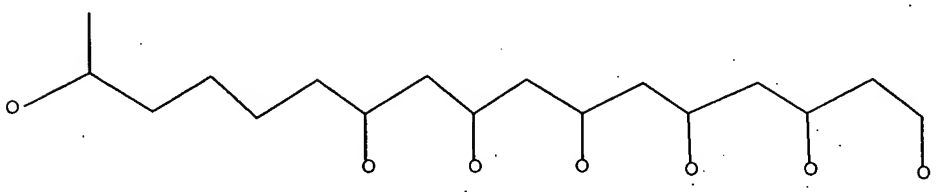
Field Availability:

Code	Name	Occurrence

1. Chakraborty, T. K.; Dutta, S., Tetrahedron Lett., CODEN: TELEAY, 39(1-2), <1998>, 101-104; BABS-6085475

L25 ANSWER 23 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN):	1965671
Chemical Name (CN):	heptadecane-1,3,5,7,9,11,16-heptaol
Autonom Name (AUN):	heptadecane-1,3,5,7,9,11,16-heptaol
Molec. Formula (MF):	C17 H36 O7
Molecular Weight (MW):	352.47
Lawson Number (LN):	687
Compound Type (CTYPE):	acyclic
Constitution ID (CONSID):	1838397
Tautomer ID (TAUTID):	1903620
Beilstein Citation (BSO):	5-01
Entry Date (DED):	1989/06/29
Update Date (DUPD):	1997/12/03



Field Availability:

Code	Name	Occurrence
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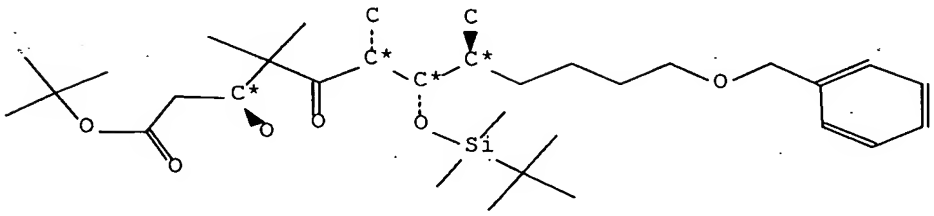
BPR	Beilstein Preferred RN	1
RN	CAS Registry Number	1
CN	Chemical Name	1
AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
DED	Entry Date	1
DUPD	Update Date	1
IR	Infrared Spectrum	1
MP	Melting Point	1
MS	Mass Spectrum	1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence

Chemical Name (CN):	12-benzyloxy-7-(tert-butyl-dimethyl-silanyloxy)-3-hydroxy-4,4,6,8-tetramethyl-5-oxo-dodecanoic acid tert-butyl ester
Autonom Name (AUN):	12-benzyloxy-7-(tert-butyl-dimethyl-silanyloxy)-3-hydroxy-4,4,6,8-tetramethyl-5-oxo-dodecanoic acid tert-butyl ester
Molec. Formula (MF):	C33 H58 O6 Si
Molecular Weight (MW):	578.90
Lawson Number (LN):	5228, 3798, 3777, 2672, 318
File Segment (FS):	Stereo compound
Compound Type (CTYPE):	isocyclic
Constitution ID (CONSID):	6834281
Tautomer ID (TAUTID):	7583399
Beilstein Citation (BSO):	6-06
Entry Date (DED):	1998/11/09
Update Date (DUPD):	1998/11/09



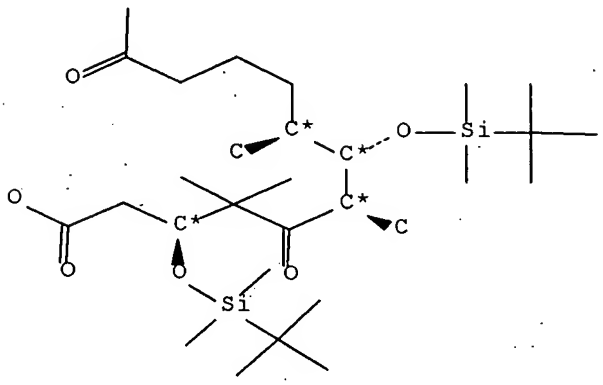
Field Availability:

Code	Name	Occurrence
BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	5
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation	1
DED	Entry Date	1
DUPD	Update Date	1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
RX	Reaction Documents	2
RXREA	Substance is Reaction Reactant	1
RXPRO	Substance is Reaction Product	1

All References:
ALLREF



Field Availability:

Code	Name	Occurrence
BRN	Beilstein Records	1
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FW	Formular Weight	1
LN	Lawson Number	3
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
DED	Entry Date	1
DUPD	Update Date	1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
RX	Reaction Documents	2
RXREA	Substance is Reaction Reactant	1
RXPRO	Substance is Reaction Product	1

All References:
ALLREF

1. Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6591064
2. Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6441824

L25 ANSWER 22 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN): 7955235

Field Availability:

Code	Name	Occurrence
BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	4
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
DED	Entry Date	1
DUPD	Update Date	1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
RX	Reaction Documents	2
RXREA	Substance is Reaction Reactant	1
RXPRO	Substance is Reaction Product	1

All References:
ALLREF

1. Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6591064
2. Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6441824

L25 ANSWER 21 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN):	9738862
Chemical Name (CN):	3,7-bis-(tert-butyl-dimethyl-silanyloxy)-4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid
Autonom Name (AUN):	3,7-bis-(tert-butyl-dimethyl-silanyloxy)-4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid
Molec. Formula (MF):	C29 H58 O6 Si2
Molecular Weight (MW):	558.94
Lawson Number (LN):	3798, 3777, 2674
File Segment (FS):	Stereo compound
Compound Type (CTYPE):	acyclic
Constitution ID (CONSID):	8203590
Tautomer ID (TAUTID):	9128603
Entry Date (DED):	2004/10/23
Update Date (DUPD):	2007/02/05

CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
DED	Entry Date	1
DUPD	Update Date	1

This substance also occurs in Reaction Documents:

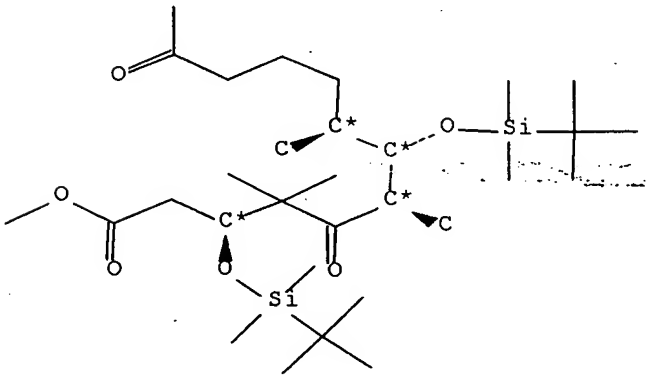
Code	Name	Occurrence
RX	Reaction Documents	2
RXREA	Substance is Reaction Reactant	1
RXPRO	Substance is Reaction Product	1

All References:
ALLREF

1. Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6591064
2. Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6441824

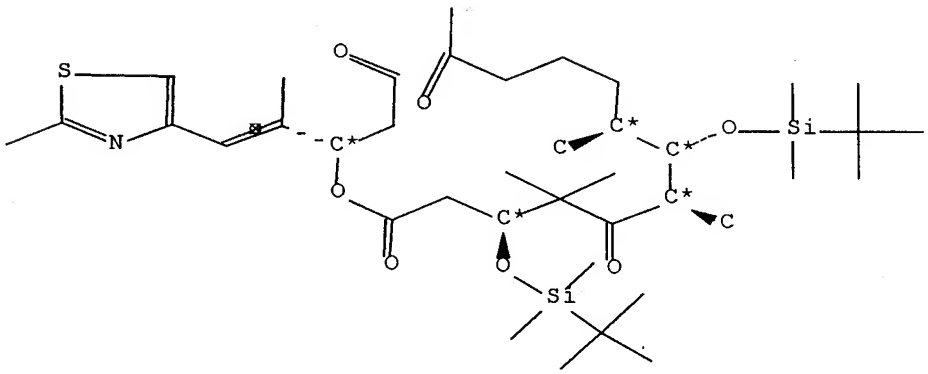
L25 ANSWER 20 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN):	9738952
Chemical Name (CN):	3,7-bis-(tert-butyl-dimethyl-silanyloxy)-4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid methyl ester
Autonom Name (AUN):	3,7-bis-(tert-butyl-dimethyl-silanyloxy)-4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid methyl ester
Molec. Formula (MF):	C30 H60 O6 Si2
Molecular Weight (MW):	572.97
Lawson Number (LN):	3798, 3777, 2674, 289
File Segment (FS):	Stereo compound
Compound Type (CTYPE):	acyclic
Constitution ID (CONSID):	8203696
Tautomer ID (TAUTID):	9128457
Entry Date (DED):	2004/10/23
Update Date (DUPD):	2007/02/05



L25 ANSWER 19 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

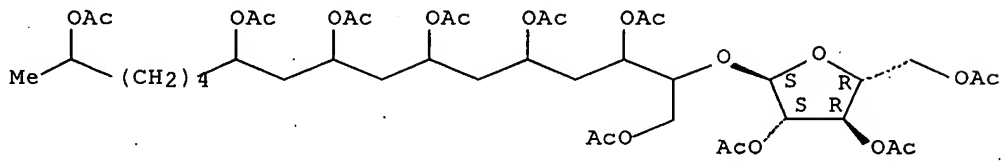
Beilstein Records (BRN):	9747518
Chemical Name (CN):	3,7-bis-(tert-butyl-dimethyl-silanyloxy)-4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid 2-methyl-3-(2-methyl-thiazol-4-yl)-1-(2-oxo-ethyl)-allyl ester
Autonom Name (AUN):	3,7-bis-(tert-butyl-dimethyl-silanyloxy)-4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid 2-methyl-3-(2-methyl-thiazol-4-yl)-1-(2-oxo-ethyl)-allyl ester
Molec. Formula (MF):	C39 H69 N O7 S Si2
Molecular Weight (MW):	752.21
Lawson Number (LN):	31322, 3798, 3777, 2674
File Segment (FS):	Stereo compound
Compound Type (CTYPE):	heterocyclic
Constitution ID (CONSID):	8211765
Tautomer ID (TAUTID):	9136618
Entry Date (DED):	2004/10/23
Update Date (DUPD):	2007/02/05



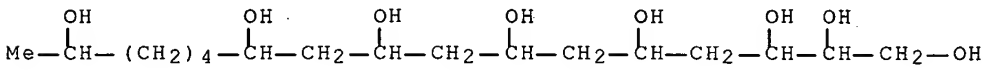
Field Availability:

Code	Name	Occurrence
BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	4
FS	File Segment	1

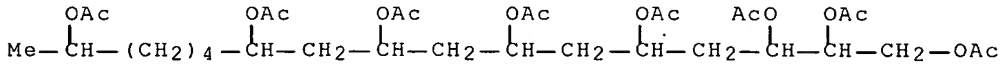
Absolute stereochemistry.



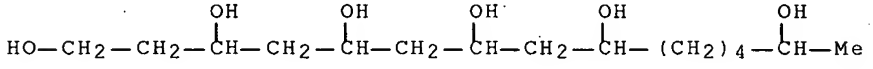
RN 53294-58-9 ZCAPLUS
CN 1,2,3,5,7,9,11,16-Heptadecaneoctol (9CI) (CA INDEX NAME)



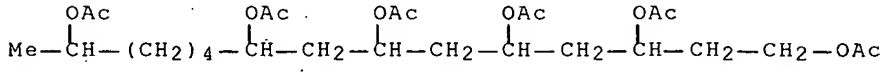
RN 53294-63-6 ZCAPLUS
CN 1,2,3,5,7,9,11,16-Heptadecaneoctol, octaacetate (9CI) (CA INDEX NAME)



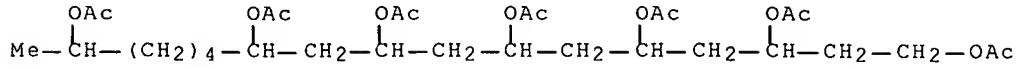
RN 53294-64-7 ZCAPLUS
CN 1,3,5,7,9,14-Pentadecanehexol (9CI) (CA INDEX NAME)



RN 53294-65-8 ZCAPLUS
CN 1,3,5,7,9,14-Pentadecanehexol, hexaacetate (9CI) (CA INDEX NAME)



RN 53294-66-9 ZCAPLUS
CN 1,3,5,7,9,11,16-Heptadecaneheptol, heptaacetate (9CI) (CA INDEX NAME)



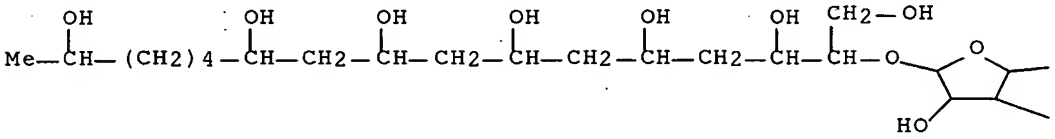
AB The structures of secopyrimycins A [MeO2CCHBuCH(OH)CHMe(CH2)2[CH(OH)(CH2)3]2[CH(O H)]2Me], B (I), and C, [AcNH(CH2)3[CH(OH)CHMe]2 CH2OH] were detd.from their high resolution mass spectra and/or those of their simplederivs. and chemical degradation products.

IT ***54799-27-8***
RL: PRP (Properties)
(mol. structure of, mass spectrum in relation to)

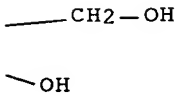
RN 54799-27-8 ZCAPLUS

CN 1,3,5,7,9,11,16-Heptadecaneheptol, 2-(α-D-arabinofuranosyloxy)-(9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 1-B



L25 ANSWER 18 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1974:437769 ZCAPLUS Full-text
DOCUMENT NUMBER: 81:37769
TITLE: Constitution of primycin. I. Characterization, functional groups, and degradation to the secoprimycins
AUTHOR(S): Aberhart, John; Jain, Rup C.; Fehr, Theo; De Mayo, Paul; Szilagyi, Imre
CORPORATE SOURCE: Dep. Chem., Univ. West. Ont., London, ON, Can.
SOURCE: Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1974), (7), 816-26
CODEN: JCPRB4; ISSN: 0300-922X
DOCUMENT TYPE: Journal
LANGUAGE: English

GI For diagram(s), see printed CA Issue.

AB The proposed structure of primycin (I) was determined mainly from the chemical and spectral data of its degradation products.

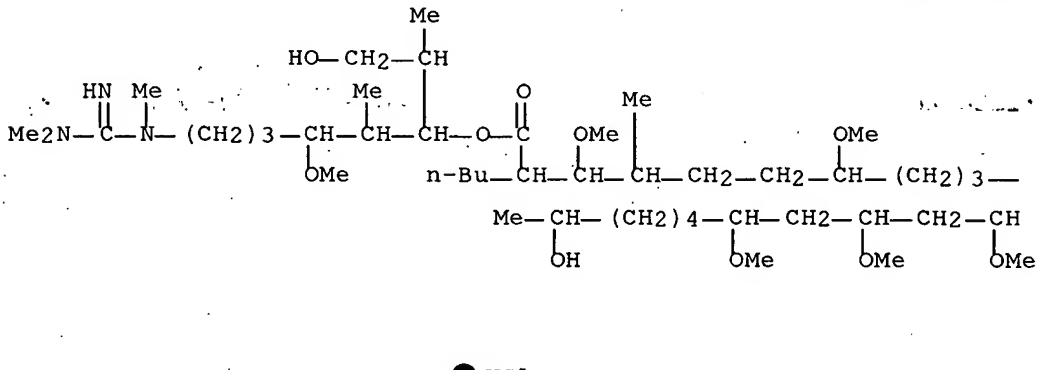
IT ***53294-56-7P 53294-58-9P 53294-63-6P***
53294-64-7P 53294-65-8P 53294-66-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 53294-56-7 ZCAPLUS

CN 1,3,5,7,9,11,16-Heptadecaneheptol, 2-[(2,3,5-tri-O-acetyl-α-D-arabinofuranosyl)oxy]-, heptaacetate (9CI) (CA INDEX NAME)

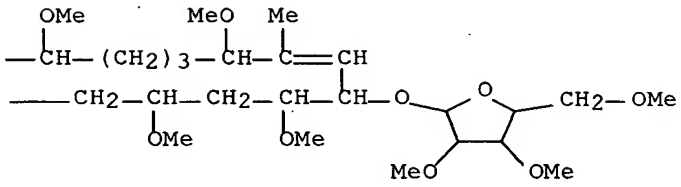
arabinofuranosyl)oxy]-, 6-[[(dimethylamino)iminomethyl]methylamino]-1-(2-hydroxy-1-methylethyl)-3-methoxy-2-methylhexyl ester, monohydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A



● HCl

PAGE 1-B



L25 ANSWER 17 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1974:436929 ZCAPLUS Full-text
DOCUMENT NUMBER: 81:36929
TITLE: Constitution of primycin. II. Mass spectra of the secoprimycins
AUTHOR(S): Gracey, D. E. Fergus; Baczynskyj, Lubomir; Martin, Trevor I.; MacLean, David B.
CORPORATE SOURCE: Dep. Chem., McMaster Univ., Hamilton, ON, Can.
SOURCE: Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1974), (7), 827-36
CODEN: JCPRB4; ISSN: 0300-922X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.

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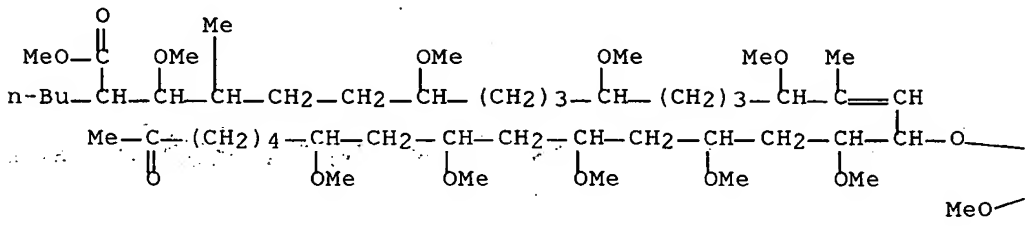
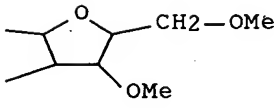
—OMe

RN 53294-05-6 ZCAPLUS
CN 16-Tritriacontenoic acid, 2-butyl-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-32-oxo-18-[(2,3,5-tri-O-methyl-α-D-arabinofuranosyl)oxy]-, methyl ester (9CI) (CA INDEX NAME)

PAGE 1-A

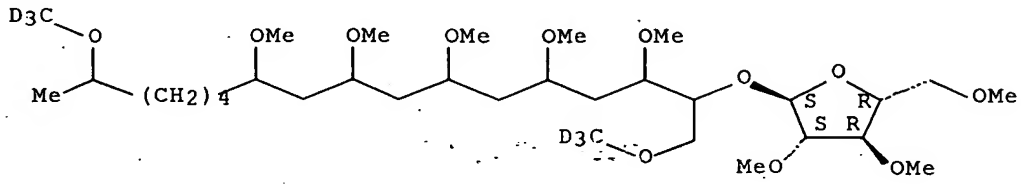


PAGE 1-B

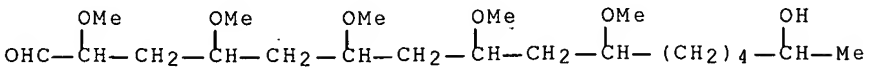


RN 53294-53-4 ZCAPLUS
CN α-D-Arabinofuranoside, 2,4,6,8,10-pentamethoxy-15-(methoxy-d3)-1-(methoxy-d3-methyl)hexadecyl 2,3,5-tri-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



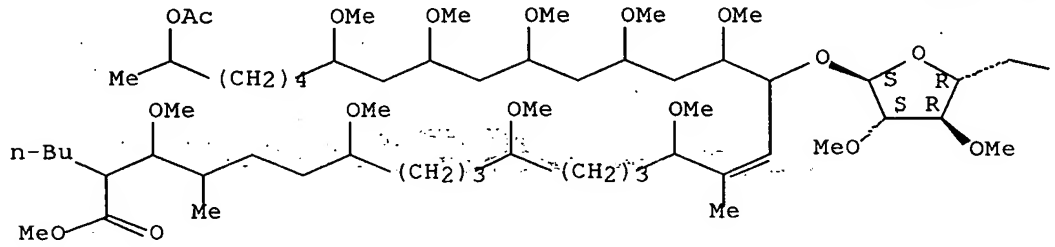
RN 53503-23-4 ZCAPLUS
CN 16-Tritriacontenoic acid, 2-butyl-32-hydroxy-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-18-[(2,3,5-tri-O-methyl-α-D-



RN 53294-03-4 ZCAPLUS
CN 16-Tritriacontenoic acid, 32-(acetyloxy)-2-butyl-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-18-[(2,3,5-tri-O-methyl-α-D-arabinofuranosyl)oxy]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A

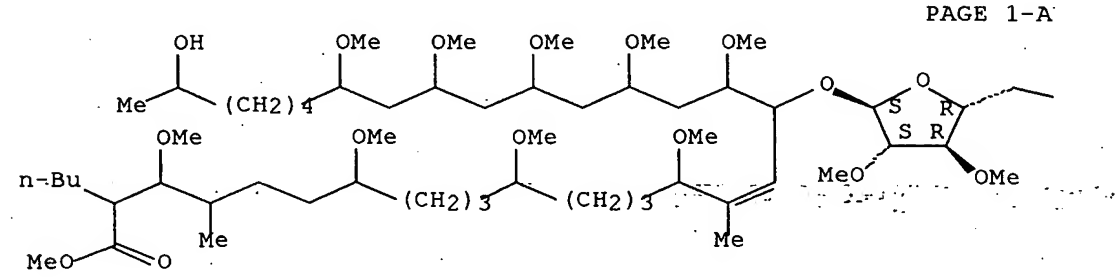


PAGE 1-B

RN 53294-04-5 ZCAPLUS
CN 16-Tritriacontenoic acid, 2-butyl-32-hydroxy-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-18-[(2,3,5-tri-O-methyl-α-D-arabinofuranosyl)oxy]-, methyl ester (9CI) (CA INDEX NAME)

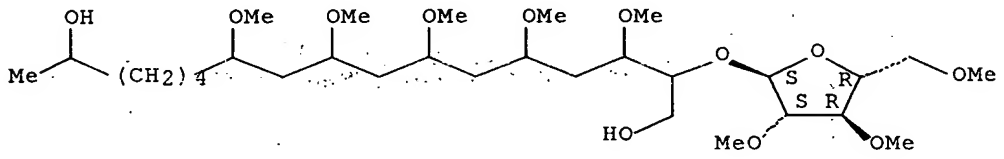
Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



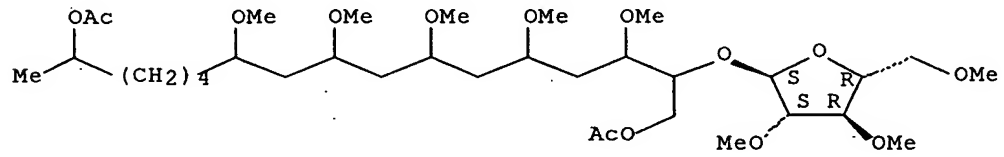
DOCUMENT TYPE: Journal
LANGUAGE: English
GI For diagram(s), see printed CA Issue.
AB Methylation of primycin (I) gave, after chromatog., the trimethylated urea and guanidine derivs. (II and III). The structure of I was determined by a spectral study of the ozonolysis products of II and III and their degradation products.
IT ***53293-97-3P 53293-98-4P 53293-99-5P 53294-00-1P 53294-03-4P 53294-04-5P 53294-05-6P 53294-53-4P 53503-23-4P***
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 53293-97-3 ZCAPLUS
CN α-D-Arabinofuranoside, 15-hydroxy-1-(hydroxymethyl)-2,4,6,8,10-pentamethoxyhexadecyl 2,3,5-tri-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

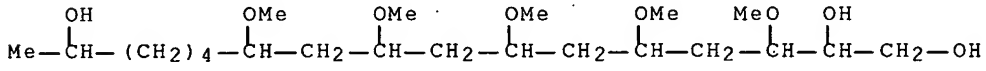


RN 53293-98-4 ZCAPLUS
CN α-D-Arabinofuranoside, 15-(acetyloxy)-1-[(acetyloxy)methyl]-2,4,6,8,10-pentamethoxyhexadecyl 2,3,5-tri-O-methyl- (9CI) (CA INDEX NAME)

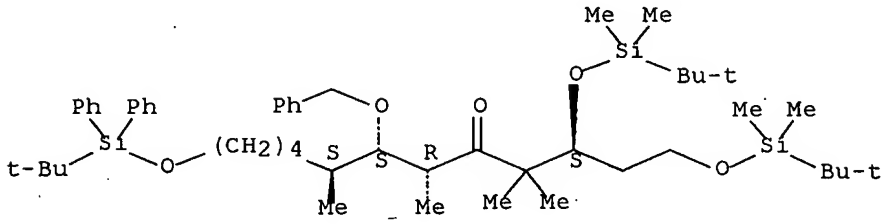
Absolute stereochemistry.



RN 53293-99-5 ZCAPLUS
CN 1,2,16-Heptadecanetriol, 3,5,7,9,11-pentamethoxy- (9CI) (CA INDEX NAME)

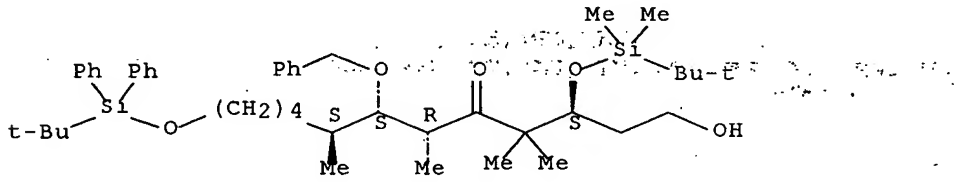


RN 53294-00-1 ZCAPLUS
CN Hexadecanal, 15-hydroxy-2,4,6,8,10-pentamethoxy- (9CI) (CA INDEX NAME)



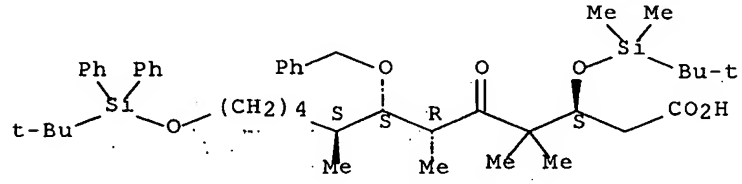
RN 197634-37-0 ZCAPLUS
CN 4,15-Dioxa-3,16-disilaoctadecan-7-one, 5-(2-hydroxyethyl)-2,2,3,3,6,6,8,10,17,17-decamethyl-16,16-diphenyl-9-(phenylmethoxy)-, [5S-(5R*,8S*,9R*,10R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

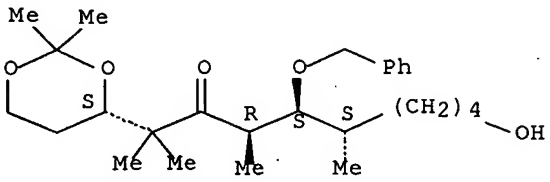


RN 197634-39-2 ZCAPLUS
CN Dodecanoic acid, 3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-12-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4,4,6,8-tetramethyl-5-oxo-7-(phenylmethoxy)-, [3S-(3R*,6S*,7R*,8R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

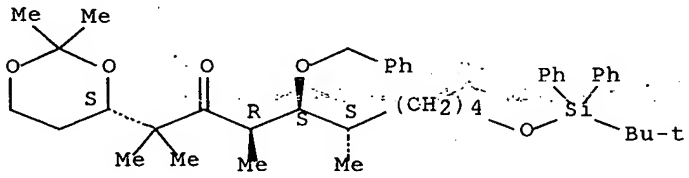


L25 ANSWER 16 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1974:463919 ZCAPLUS Full-text
DOCUMENT NUMBER: 81:63919
TITLE: Constitution of primycin. III. Degradation of methylated primycin, and the structure of primycin
AUTHOR(S): Fehr, Theo; Jain, Rup C.; De Mayo, Paul; Motl, O.; Szilagyi, Imre; Baczynskyj, Lubomir; Gracey, D. E. Fergus; Holland, Herbert L.; MacLean, David B.
CORPORATE SOURCE: Dep. Chem., Univ. West. Ont., London, ON, Can.
SOURCE: Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999) (1974), (7), 836-47
CODEN: JCPRB4; ISSN: 0300-922X



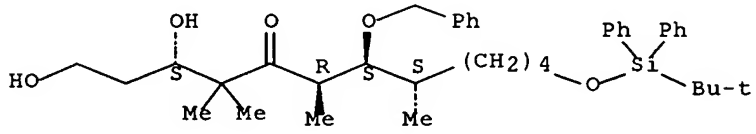
RN 197634-31-4 ZCAPLUS
CN 3-Decanone, 2-(2,2-dimethyl-1,3-dioxan-4-yl)-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,4,6-trimethyl-5-(phenylmethoxy)-, [4S-[4R*(4S*,5R*,6R*)]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



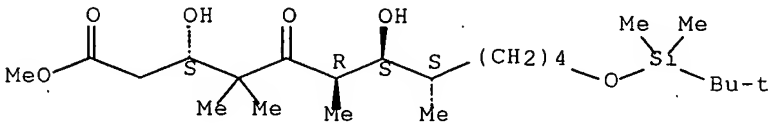
RN 197634-33-6 ZCAPLUS
CN 5-Dodecanone, 12-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1,3-dihydroxy-4,4,6,8-tetramethyl-7-(phenylmethoxy)-, [3S-(3R*,6S*,7R*,8R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 197634-35-8 ZCAPLUS
CN 4,17-Dioxa-3,18-disilaeicosan-9-one, 7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,2,3,3,8,8,10,12,19,19-decamethyl-18,18-diphenyl-11-(phenylmethoxy)-, [7S-(7R*,10S*,11R*,12R*)]- (9CI) (CA INDEX NAME)

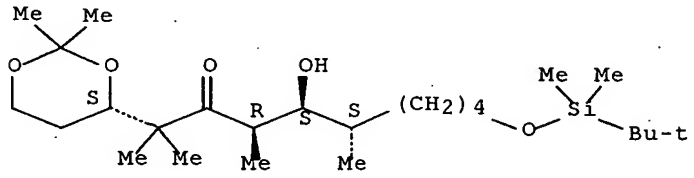
Absolute stereochemistry.



IT ***197634-28-9P 197634-29-0P 197634-30-3P***
197634-31-4P 197634-33-6P 197634-35-8P
197634-37-0P 197634-39-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediates in the total synthesis of epothilones A and B)

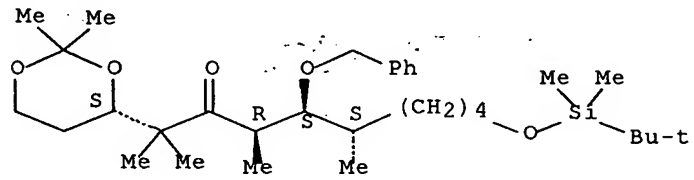
RN 197634-28-9 ZCAPLUS
CN 3-Decanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-hydroxy-2,4,6-trimethyl-, (4R,5S,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 197634-29-0 ZCAPLUS
CN 3-Decanone, 2-(2,2-dimethyl-1,3-dioxan-4-yl)-10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6-trimethyl-5-(phenylmethoxy)-, [4S-[4R*(4S*,5R*,6R*)]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 197634-30-3 ZCAPLUS
CN 3-Decanone, 2-(2,2-dimethyl-1,3-dioxan-4-yl)-10-hydroxy-2,4,6-trimethyl-5-(phenylmethoxy)-, [4S-[4R*(4S*,5R*,6R*)]]- (9CI) (CA INDEX NAME)

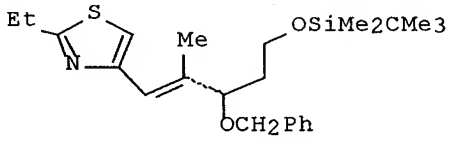
Absolute stereochemistry.

IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9721493		A	19980319	AU 1997-21493	19970115
AU 716610		B2	20000302		
EP 923583		A1	19990623	EP 1997-914077	19970115
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NZ 334821		A	20001222	NZ 1997-334821	19970115
JP 2001500851		T	20010123	JP 1998-511141	19970115
US 5969145		A	19991019	US 1997-921512	19970902
US 6043372		A	20000328	US 1999-344713	19990625
US 6156905		A	20001205	US 2000-478466	20000106
PRIORITY APPLN. INFO.:				DE 1996-19636343	A 19960830
				US 1996-27480P	P 19960926
				DE 1996-19645361	A 19961028
				DE 1996-19645362	A 19961028
				WO 1997-DE111	W 19970115
				US 1997-921512	A3 19970902
				US 1999-344713	A3 19990625

OTHER SOURCE(S): CASREACT 127:346234

GI



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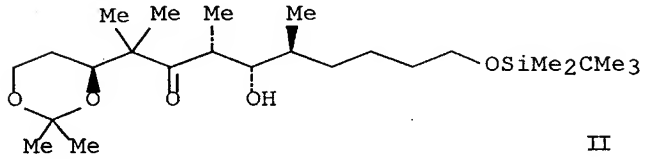


II

AB Intermediates, e.g. 2-(2,2-dimethyl-1,3-dioxan-4-yl)-2-methyl-3-pentanone, 6-[(tert-butyldimethylsilyl)oxy]-2-methylhexanal, (S,4E)-3-benzyloxy-1- (tert-butyldimethylsilyloxy)-4-methyl-5-(2-ethyl-thiazol-4-yl)-4-pentene (I), (4S,6S)-10(tert-butyldimethylsilyloxy)-2-(2,2-dimethyl-1,3-dioxan-4- yl)-5-hydroxy-2,4,6-trimethyl-3-decanone (II) and (3S,6R,7S,8S)-7- benzyloxy-3-(tert-butyldimethylsilyloxy)-12-(tert-butyldiphenylsilyloxy)- 4,4,6,8-tetramethyl-5-oxododecanoic acid, in the total synthesis of epothilones A and B are described. Epothilones A and B are natural products,.

IT ***197634-08-5P***
RL: PNU (Preparation, unclassified); PREP (Preparation)
(intermediates in the total synthesis of epothilones A and B)

RN 197634-08-5 ZCAPLUS

CN Dodecanoic acid, 12-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxo-, methyl ester, [3S-(3R*,6S*,7R*,8R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

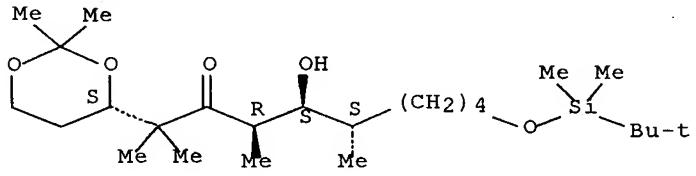
AB The title compds. [I; II; III; R1, R2 = H, alkyl, aryl, aralkyl; R3 = CH2OH, CH2OR; R4 = OH, OR; R = CR7R8; R7, R8 = H, alkyl, aryl, or R7R8 = (CH2)n; n = 2-6; R5, R6 = H, alkyl, aralkyl, or R5R6 = (CH2)m; m = 2-5; R9, R10 = H, protecting group; R11 = H, protecting group] including all the stereoisomers and their mixts. are prepared E.g., title compound (S)-III [R5 = R6 = Me, R9 = R11 = H, R10 = TBDPS] was prepared in 6 steps from D-(-)-pantolactone via reaction with 3,4-dihydro-2H-pyran, hydride reduction, Wittig reaction with methyltriphenylphosphonium bromide, protection of OH with TBDPS-Cl, de-tetrahydropyranyl, and reduction with borane-THF.

IT ***197634-28-9P***
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of new C1-C6-fragments and application for synthesis of epothilone and epothilone derivs.)

RN 197634-28-9 ZCAPLUS

CN 3-Decanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-hydroxy-2,4,6-trimethyl-, (4R,5S,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 15 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:708545 ZCAPLUS Full-text
DOCUMENT NUMBER: 127:346234
TITLE: Intermediate products within the total synthesis of Epothilones A and B
INVENTOR(S): Schinzer, Dieter; Limberg, Anja; Boehm, Oliver M.
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger., 14 pp.
CODEN: GWXXAW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19636343	C1	19971023	DE 1996-19636343	19960830
DE 19645361	A1	19980430	DE 1996-19645361	19961028
WO 9808849	A1	19980305	WO 1997-DE111	19970115

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR,

TITLE: New (C1-C6)-fragments, method for their preparation and their application for synthesis of epothilone and epothilone derivatives

INVENTOR(S): Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd; Schirner, Michael

PATENT ASSIGNEE(S): Schering A.-G., Germany

SOURCE: Ger. Offen., 18 pp.
CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19735578	A1	19990211	DE 1997-19735578	19970809
CA 2299608	A1	19990218	CA 1998-2299608	19980810
WO 9907692	A2	19990218	WO 1998-EP5064	19980810
WO 9907692	A3	19990514		
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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9893409	A	19990301	AU 1998-93409	19980810
EP 1005465	A2	20000607	EP 1998-946309	19980810
EP 1005465	B1	20070725		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, AL, MK				
JP 2001512723	T	20010828	JP 2000-506196	19980810
AT 368036	T	20070815	AT 1998-946309	19980810
US 2003144523	A1	20030731	US 2000-485292	20000503

PRIORITY APPLN. INFO.:

DE 1997-19735574	A	19970809
DE 1997-19735575	A	19970809
DE 1997-19735578	A	19970809
DE 1997-19748928	A	19971024
DE 1997-19749717	A	19971031
DE 1997-19751200	A	19971113
DE 1998-19813821	A	19980320
WO 1998-EP5064	W	19980810

OTHER SOURCE(S): CASREACT 130:168164; MARPAT 130:168164

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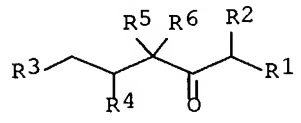

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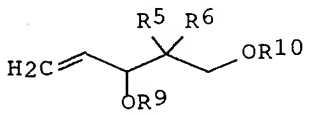

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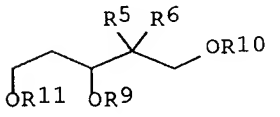
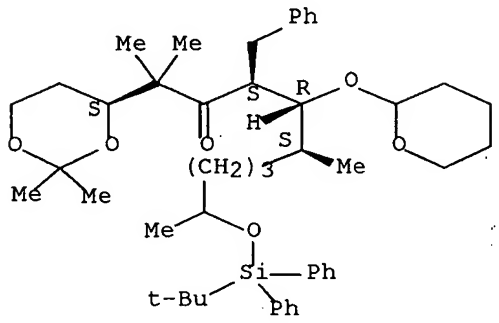


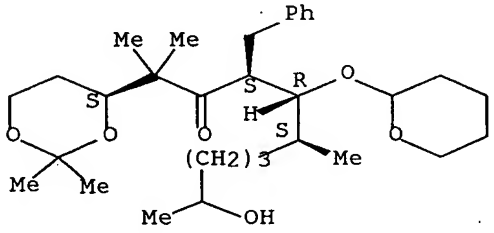
III

Absolute stereochemistry.



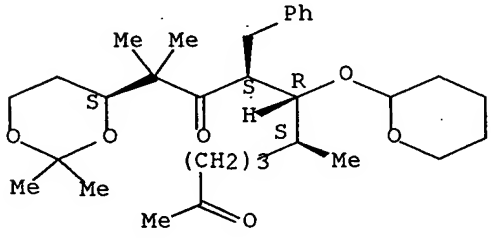
RN 220774-78-7 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-4-(phenylmethyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4S,5R,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

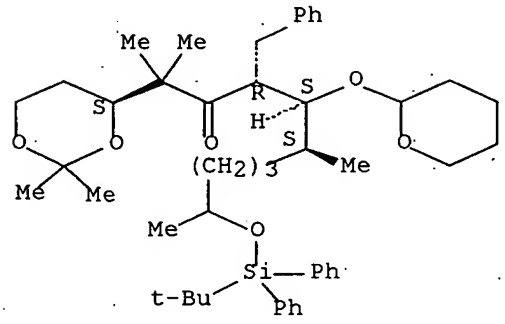


RN 220774-80-1 ZCAPLUS
CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-8-(phenylmethyl)-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7R,8S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

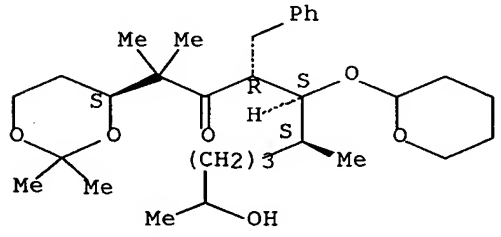


L25 ANSWER 14 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:116659 ZCAPLUS Full-text
DOCUMENT NUMBER: 130:168164



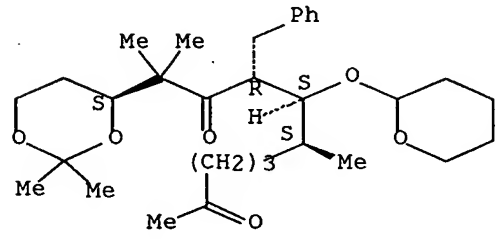
RN 220774-61-8 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-4-(phenylmethyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



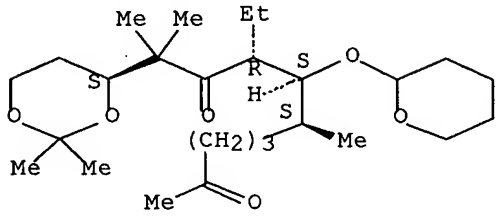
RN 220774-62-9 ZCAPLUS
CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-8-(phenylmethyl)-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



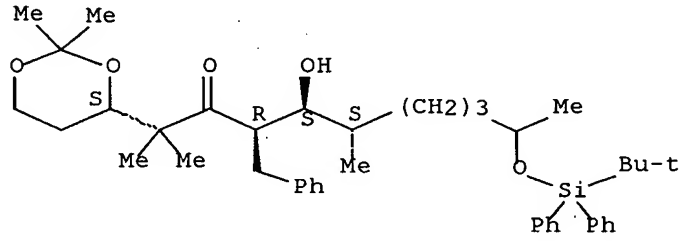
RN 220774-76-5 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-4-(phenylmethyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



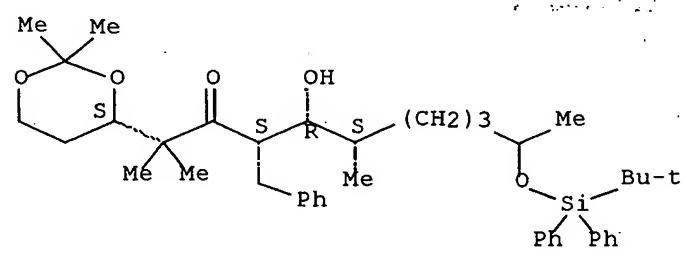
RN 220774-58-3 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(phenylmethyl)-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 220774-59-4 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(phenylmethyl)-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

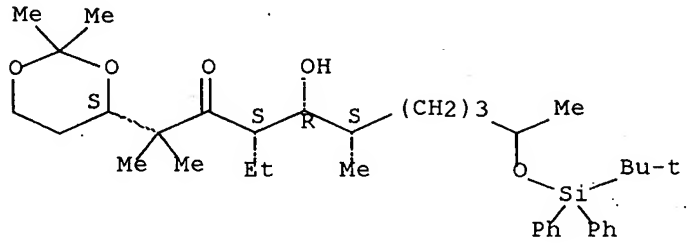
Absolute stereochemistry.



RN 220774-60-7 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-4-(phenylmethyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

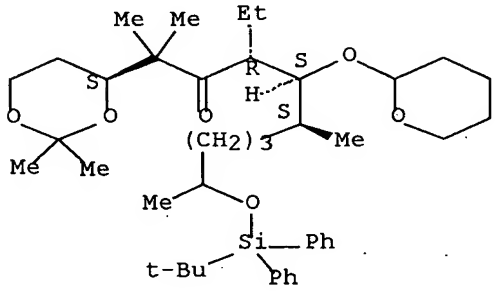
Absolute stereochemistry.

Absolute stereochemistry.



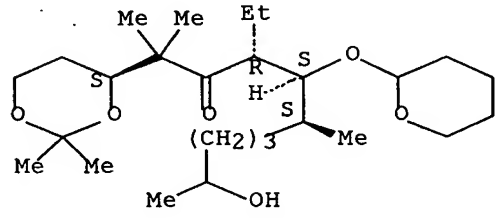
RN 220774-21-0 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 220774-22-1 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-4-ethyl-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 220774-23-2 ZCAPLUS
CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-8-ethyl-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

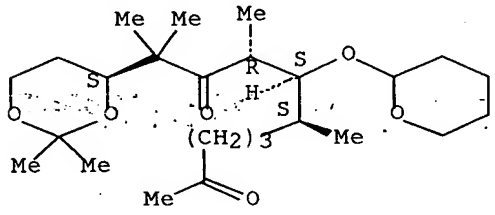
melanoma, and acute lymphocytic and myelocytic leukemia. They are also suited for anti-angiogenesis therapy and for the treatment of chronic inflammatory diseases (psoriasis, arthritis). To prevent uncontrolled cell growth on, and for better tolerability of, medical implants, the derivs. can be introduced into or applied to polymeric materials. The compds. provided for in the invention can be used alone or, to achieve additive or synergistic effects, in combination with other principles and substance categories used in tumor therapy.

IT ***220775-76-8***
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of epothilone derivs. as antitumor agents)

RN 220775-76-8 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,8,10-trimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

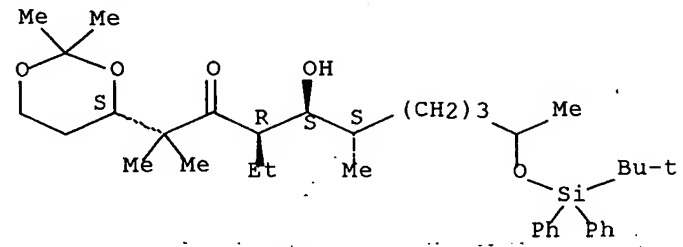


IT ***220774-19-6P 220774-20-9P 220774-21-0P***
220774-22-1P 220774-23-2P 220774-58-3P
220774-59-4P 220774-60-7P 220774-61-8P
220774-62-9P 220774-76-5P 220774-78-7P
220774-80-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of epothilone derivs. as antitumor agents)

RN 220774-19-6 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 220774-20-9 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

DE 19735575	A1	19990211	DE 1997-19735575	19970809
DE 19735578	A1	19990211	DE 1997-19735578	19970809
DE 19748928	A1	19990429	DE 1997-19748928	19971024
DE 19749717	A1	19990506	DE 1997-19749717	19971031
DE 19751200	A1	19990520	DE 1997-19751200	19971113
DE 19813821	A1	19990923	DE 1998-19813821	19980320
CA 2299608	A1	19990218	CA 1998-2299608	19980810
AU 9893409	A	19990301	AU 1998-93409	19980810
EP 1005465	A2	20000607	EP 1998-946309	19980810
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JP 2001512723	T	20010828	JP 2000-506196	19980810
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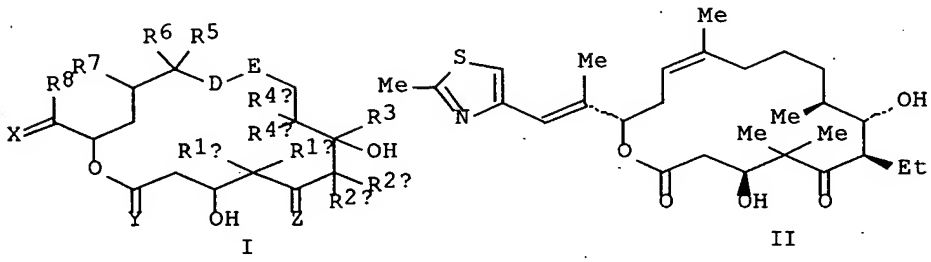
US 2003144523	A1	20030731	US 2000-485292	20000503
IN 2002DE01305	A	20050311	IN 2002-DE1305	20021227

PRIORITY APPLN. INFO.:

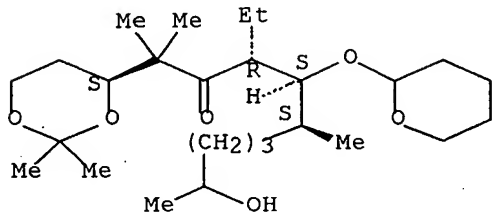
DE 1997-19735574	A	19970809
DE 1997-19735575	A	19970809
DE 1997-19735578	A	19970809
DE 1997-19748928	A	19971024
DE 1997-19749717	A	19971031
DE 1997-19751200	A	19971113
DE 1998-19813821	A	19980320
WO 1998-EP5064	W	19980810

OTHER SOURCE(S): MARPAT 130:196529

GI

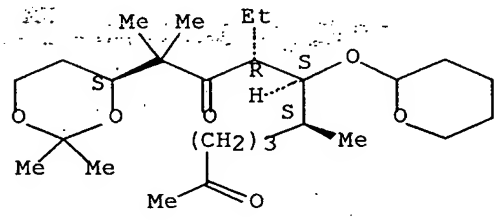


AB Epothilone derivs. of formula I [X = O, alkylene-α,ω-dioxy, two alkoxy groups, etc.; Y = O, H2; Z = O, (H, OH), (H, protected OH); R1a, R1b = H, alkyl, aryl, aralkyl, or together = (CH2)m where m = 2, 3, 4, 5; R2a, R2b = H, alkyl, aryl, aralkyl, or together = (CH2)n where n = 2, 3, 4, 5; when D-E = CH2CH2 or when Y = O, R2a or R2b may not be H/Me; R3 = H, alkyl, aryl, aralkyl; R4a, R4b = H, alkyl, aryl, aralkyl, or together = (CH2)p where p = 2, 3, 4, 5; D-E = CH2CH2, CH:CH, C.tplbond.C, 2,3-oxiranediyl, CH(OH)CH(OH), CH(OH)CH2; R5 = H, alkyl, aryl, aralkyl; R6, R7 = H, together = a saturated bond or O; R8 = H, alkyl, aryl, aralkyl all of which may be substituted] are prepared Thus, the title compds. (4S,7R,8S,9S,13E,16S(E))- and (4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-7- ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-tetramethylcyclohexadec-13-en-2,6-dione (II) were prepared in many steps. The new compds. interact with tubulin by stabilizing formed microtubuli. They are capable of influencing cell division in a phase-specific manner and are suitable for the treatment of malignant tumors, such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant



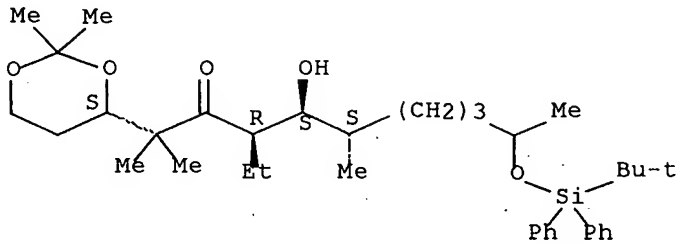
RN 220774-23-2 ZCAPLUS
CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-8-ethyl-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



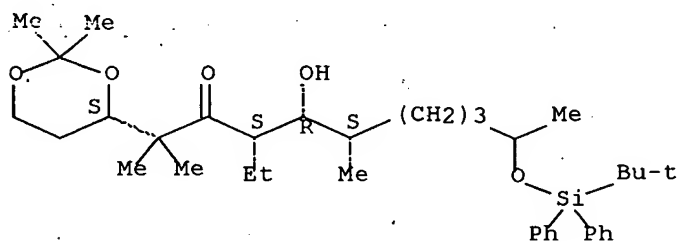
L25 ANSWER 13 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:126888 ZCAPLUS Full-text
DOCUMENT NUMBER: 130:196529
TITLE: Preparation of new epothilone derivatives as pharmaceutical agents
INVENTOR(S): Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd; Schirner, Michael
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 185 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9907692	A2	19990218	WO 1998-EP5064	19980810
WO 9907692	A3	19990514		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19735574	A1	19990211	DE 1997-19735574	19970809



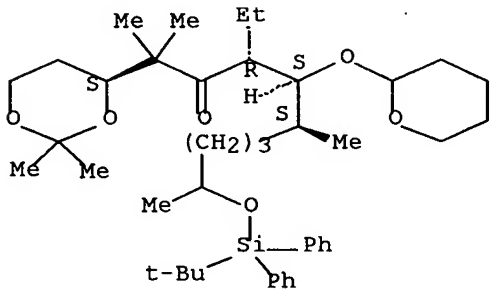
RN 220774-20-9 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



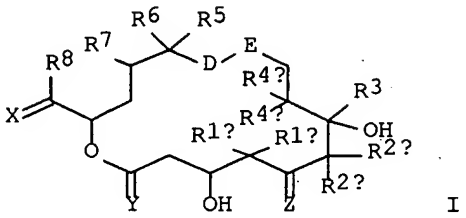
RN 220774-21-0 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 220774-22-1 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-4-ethyl-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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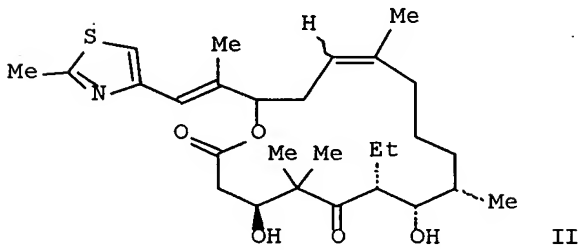


II

AB New epothilone derivs. I (R1a,R1b = R2a,R2b = same or different H, alkyl, aryl, aralkyl or (CH2)m,n m, n = 2-5; R3 = H, alkyl, aryl, aralkyl; R4a,R4b = same or different H, alkyl, aryl, aralkyl or (CH2)p = 2-5, CH2CH2, CH=CH, C.tplbond.C, epoxy, CH(OH)CH(OH), CH(OH)CH2; D-E = a group; R5 = H, alkyl, aryl, aralkyl; R6,R7 = H, bond, O; R8 = H, alkyl, aryl, aralkyl; X = O, OR23 alkylene-α,-ω-dioxy group straight or branched, OR9 or the CR10R11 group where R23 = alkyl, R9 = H or protecting group and R10,R11 = same or different H, alkyl, aryl, aralkyl or R10,R11 = together with methylene are a 5-7 membered carbocyclic ring; Y = O or two H; Z = O or H/OR12 and R12 = H or a protecting group) were prepared Thus E- and Z-II were prepared via a multistep synthesis. I cooperate with tubulin by stabilizing formed microtubuli. I are able phase specifically to affect the cell division and are suitable for the treatment of malignant ovarian, stomach, colon, adeno, breast, lung, head and neck tumors, malignant melanomas, acute lymphocytic and myelocytic leukemia. Derivs. of I are suitable for use in anti-angiogenic therapy as well as for treating chronic inflammatory diseases (psoriasis, arthritis). In order to prevent uncontrolled cell proliferations and to improve the compatibility of medical implants I can be applied or incorporated into polymeric materials. I can be used alone or to achieve additive or synergistic effects in combination with further principles and substance classes applicable in tumor therapy.

IT ***220774-19-6P 220774-20-9P 220774-21-0P 220774-22-1P 220774-23-2P***

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

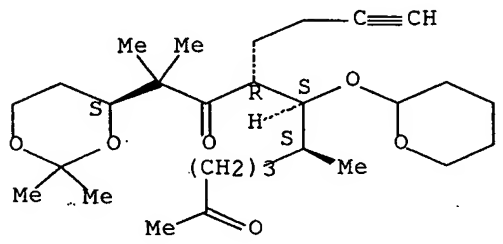
(preparation of new epothilone derivs. and their pharmaceutical uses)

RN 220774-19-6 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

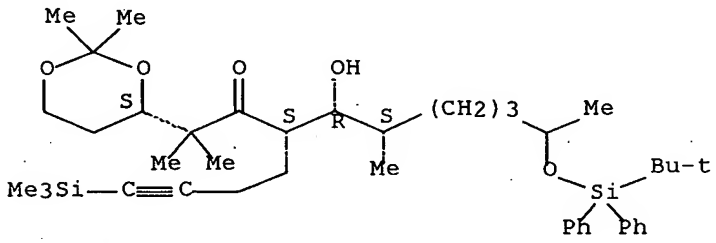
Absolute stereochemistry.

Absolute stereochemistry.



IT ***303154-57-6P***
RL: SPN (Synthetic preparation); PREP (Preparation)
(6-alkenyl and 6-alkynyl derivs. of epothilone)
RN 303154-57-6 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 12 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:738730 ZCAPLUS Full-text
DOCUMENT NUMBER: 133:309795
TITLE: Preparation of new epothilone derivatives and their pharmaceutical uses
INVENTOR(S): Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd; Schirner, Michael
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 74 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19908767	A1	20001019	DE 1999-19908767	19990218
PRIORITY APPLN. INFO.:			DE 1999-19908767	19990218

OTHER SOURCE(S): MARPAT 133:309795
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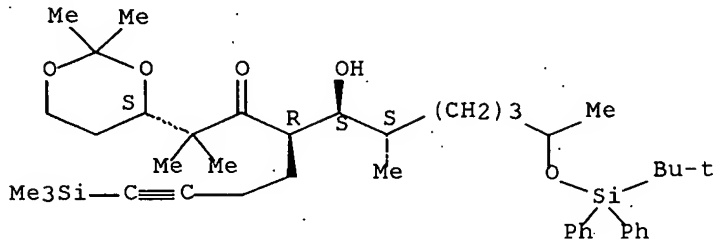
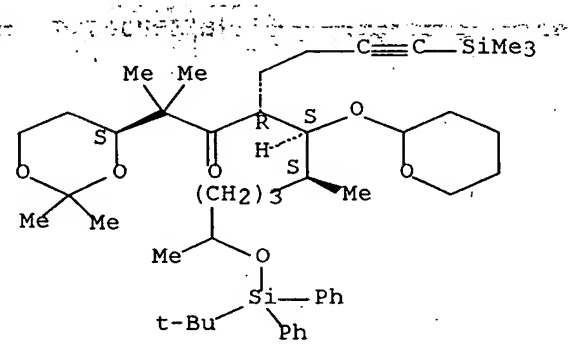


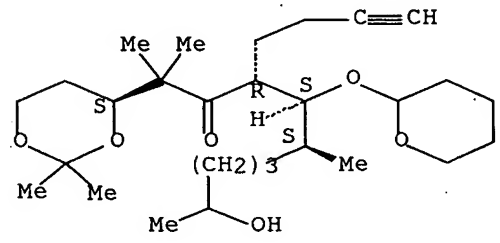
RN 303154-58-7 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 303154-59-8 ZCAPLUS
CN 3-Undecanone, 4-(3-butynyl)-2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 303154-60-1 ZCAPLUS
CN 2,9-Undecanedione, 8-(3-butynyl)-10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

BR 2000010190	A	20020108	BR 2000-10190		20000501
EP 1173441	A1	20020123	EP 2000-922826		20000501
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HU 200201010	A2	20020828	HU 2002-1010		20000501
JP 2002543203	T	20021217	JP 2000-615619		20000501
EE 200100568	A	20030217	EE 2001-568		20000501
NZ 514989	A	20040227	NZ 2000-514989		20000501
AU 772750	B2	20040506	AU 2000-43103		20000501
IN 2001MN01305	A	20070504	IN 2001-MN1305		20011019
BG 106053	A	20020531	BG 2001-106053		20011026
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MX 2001PA11039	A	20030630	MX 2001-PA11039		20011030
ZA 2001009859	A	20030228	ZA 2001-9859		20011129
US 7125893	B1	20061024	US 2002-979939		20020606
US 2005113429	A1	20050526	US 2004-965802		20041018
IN 2005MN00837	A	20070608	IN 2005-MN837		20050802
US 2006046997	A1	20060302	US 2005-214988		20050831
JP 2007224038	A	20070906	JP 2007-104224		20070411
PRIORITY APPLN. INFO.:			DE 1999-19921086	A	19990430
			DE 1999-19954228	A	19991104
			DE 2000-10013363	A	20000309
			DE 2000-10015836	A	20000327
			JP 2000-615619	A3	20000501
			WO 2000-IB657	W	20000501
			IN 2001-MN1305	A3	20011019
			US 2002-979939	A3	20020606

OTHER SOURCE(S): MARPAT 133:321769

AB The title compds. were prepared by various combinations of 3 fragments making up the mols. Thus, [4S,7R,8S,9S,13Z,16S(E)]-4,8-dihydroxy-16-[1- methyl-2-(2-pyridyl)ethenyl]-1-oxa-5,5,9,13-tetramethyl-7-(3-butynyl)-13- cyclohexadecene-2,6-dione was prepared in several steps starting from (4S)-4-(2-methyl-1-oxo-2-propyl)-2,2-dimethyl[1,3]dioxane and 5-(trimethylsilyl)-4-pentynylmagnesium bromide.

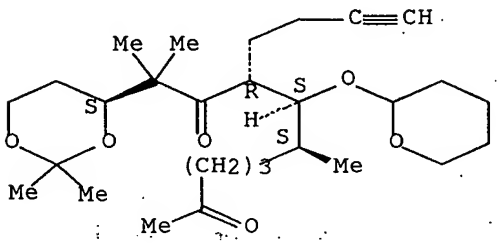
IT ***303154-56-5P 303154-58-7P 303154-59-8P 303154-60-1P***
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(6-alkenyl and 6-alkynyl derivs. of epothilone)

RN 303154-56-5 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

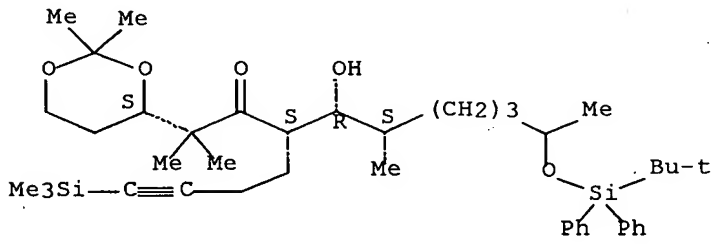
Absolute stereochemistry.

Absolute stereochemistry.



IT ***303154-57-6P***
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of 6-alkenyl-, 6-alkynyl- and 6-epoxyepothilone derivs. and their use in pharmaceutical prepns.)
RN 303154-57-6 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

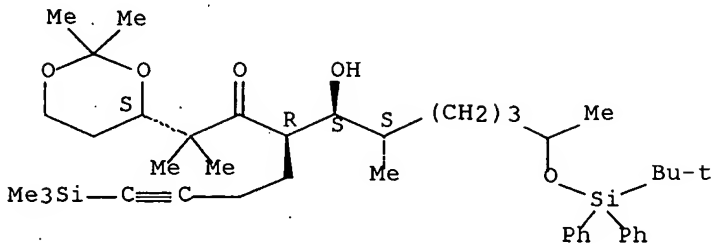
Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

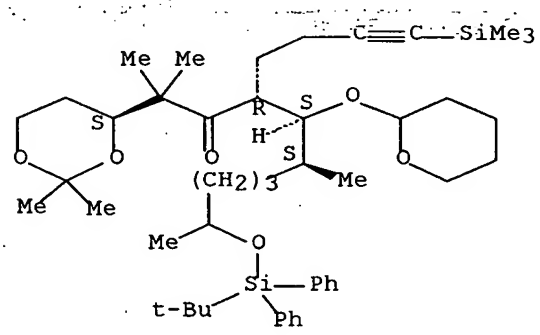
L25 ANSWER 11 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:772379 ZCAPLUS Full-text
DOCUMENT NUMBER: 133:321769
TITLE: 6-Alkenyl and 6-alkynyl derivatives of epothilone
INVENTOR(S): Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd; Hoffmann, Jens; Lichtner, Rosemarie
PATENT ASSIGNEE(S): Schering A.-G., Germany
SOURCE: Ger. Offen., 18 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19921086	A1	20001102	DE 1999-19921086	19990430
CA 2371226	A1	20001109	CA 2000-2371226	20000501
WO 2000066589	A1	20001109	WO 2000-IB657	20000501



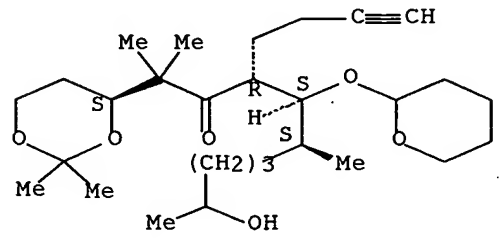
RN 303154-58-7 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 303154-59-8 ZCAPLUS
CN 3-Undecanone, 4-(3-butynyl)-2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 303154-60-1 ZCAPLUS
CN 2,9-Undecanedione, 8-(3-butynyl)-10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

DE 1999-19954228	A1	19991104
DE 2000-10015836	A1	20000327
DE 2000-10013363	A	20000309
WO 2000-IB657	W	20000501
IN 2001-MN1305	A3	20011019
US 2002-979939	A3	20020606

OTHER SOURCE(S): MARPAT 133:362656
GI

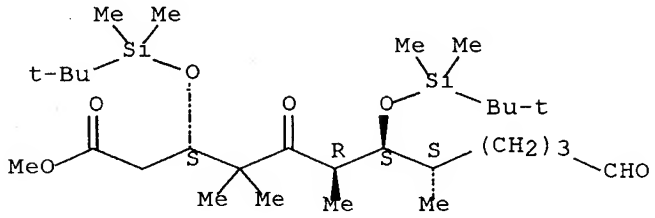
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The antitumor agents, 6-alkenyl-, 6-alkynyl- and 6-epoxyepothilones I (R1a, R1b are same or different = H, C1-C10 alkyl, C6-C12 aryl, C7-C20 aralkyl each optionally substituted; or together = (CH2)m m = 1-5 or -CH2OCH2-; R2a(R2b replace a with b) = H, substituted alkyl, aryl, aralkyl, (CH2)ra-C.tplbond.(or =)C-(CH2)pa-R26a, Q, Q1 where n = 0-5; ra, rb = the same or different and = 0-4; pa, pb = the same or different and = 0-3; R3a = H, substituted alkyl, aryl or aralkyl; R3b = OH, OPG14; R14 = H, OR14a, halogen and R14a = H, SO2-alkyl, SO2-aryl or SO2-aralkyl; R4 = H, substituted alkyl, aryl or aralkyl, halogen, OR25, CN; R26a, R26b = same or different = H, substituted alkyl, aryl or aralkyl, C1-C10 acyl or if pa or pb > 0, addnl. a group OR27; R25 = R27 = R22 = H, PG; R5 = H, substituted alkyl, aryl or aralkyl, (CH2)sT s = 1-4, T = OR22 or halogen; R6, R7 = H or together = bond or O; G = X=CR8 or bi- or tricyclic aryl radical and R8 = H, halogen, CN, or substituted alkyl, aryl or aralkyl; X = O, two OR23 groups, C2-C10-alkylene-α,ω-dioxy straight chain or branched; H/OR9 or CR10R11 group and R23 = alkyl radical, R9 = H, PG, R10,R11 = same or different = H, substituted alkyl, aryl or aralkyl, or together with the methylene are a 5-7 carbocyclic ring; D-E = CH2CH2 or OCH2; A = OC(O), OCH2, CH2C(O), NR29C(O), NR29SO2 and R29 = H, alkyl; Z = O or H/OR12 and R12 = H, PG) were prepared Thus II was prepared in a multistep synthesis starting from (4S)-4-(2-methyl-1-oxoprop-2-yl)-2,2- dimethyl[1,3]dioxane and 5-trimethylsilylpent-4-in-1-yl magnesium bromide. II had an IC50 value [nM] of 3.0 for the growth inhibition of human MCF-7 breast- and 75 for multidrug resistant NCI/ADR carcinoma cell lines with a selectivity of 2.5. The new epothilone derivs. interact with tubulin by stabilizing microtubuli that are formed. They are able to influence the cell-splitting in a phase-specific manner and are therefore useful in treating diseases or conditions associated with the need for cell growth, division and/or proliferation. Thus the epothilone derivs. are suitable for treating malignant tumors, e.g., ovarian, stomach, colon, adeno-, breast, lung, head and neck carcinomas, malignant melanoma, acute lymphocytic and myelocytic leukemia; and for anti-angiogenesis therapy as well as for treatment of chronic inflammatory diseases (such as psoriasis, arthritis).

IT ***303154-56-5P 303154-58-7P 303154-59-8P***
303154-60-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of 6-alkenyl-, 6-alkynyl- and 6-epoxyepothilone derivs. and their use in pharmaceutical prepns.)

RN 303154-56-5 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 10 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:790507 ZCAPLUS Full-text
DOCUMENT NUMBER: 133:362656
TITLE: Preparation of 6-alkenyl-, 6-alkynyl- and 6-epoxyepothilone derivatives and their antitumor activity
INVENTOR(S): Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd; Hoffmann, Jens; Lichtner, Rosemarie
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 298 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066589	A1	20001109	WO 2000-IB657	20000501
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 19921086	A1	20001102	DE 1999-19921086	19990430
DE 19954228	A1	20010913	DE 1999-19954228	19991104
DE 10015836	A1	20011011	DE 2000-10015836	20000327
CA 2371226	A1	20001109	CA 2000-2371226	20000501
BR 2000010190	A	20020108	BR 2000-10190	20000501
EP 1173441	A1	20020123	EP 2000-922826	20000501
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002543203	T	20021217	JP 2000-615619	20000501
EE 200100568	A	20030217	EE 2001-568	20000501
NZ 514989	A	20040227	NZ 2000-514989	20000501
AU 772750	B2	20040506	AU 2000-43103	20000501
IN 2001MN01305	A	20070504	IN 2001-MN1305	20011019
BG 106053	A	20020531	BG 2001-106053	20011026
NO 2001005278	A	20011221	NO 2001-5278	20011029
MX 2001PA11039	A	20030630	MX 2001-PA11039	20011030
US 7125893	B1	20061024	US 2002-979939	20020606
IN 2005MN00837	A	20070608	IN 2005-MN837	20050802
US 2006046997	A1	20060302	US 2005-214988	20050831
PRIORITY APPLN. INFO.:			DE 1999-19921086	A1 19990430

PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001073103	A2	20011004	WO 2001-US9620	20010323
WO 2001073103	A3	20020523		
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002042109	A1	20020411	US 2001-811808	20010319
US 6593115	B2	20030715		
US 2004023345	A1	20040205	US 2003-447082	20030528
PRIORITY APPLN. INFO.:			US 2000-191975P	P 20000324
			US 2001-811808	A3 20010319

OTHER SOURCE(S): CASREACT 135:287591; MARPAT 135:287591

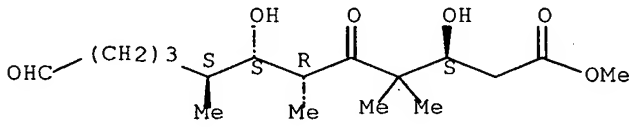
AB The present invention relates to a process for the preparation of intermediates useful in the synthesis of epothilone analogs by initially enzymically degrading certain epothilone compds. to form ring-open structures containing a carboxyl group which is esterified, the hydroxyl groups on the moiety protected and the resulting compound oxidized by, e.g. ozone, to form a first intermediate. The first intermediate can be reacted with a triphenylphosphine adduct to yield a compound containing an ester group at position 1 which is subsequently hydrolyzed to form a second intermediate.

IT ***364336-79-8P 364336-83-4P***
RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of epothilone intermediates)

RN 364336-79-8 ZCAPLUS

CN Dodecanoic acid, 3,7-dihydroxy-4,4,6,8-tetramethyl-5,12-dioxo-, methyl ester, (3S,6R,7S,8S)- (9CI) (CA INDEX NAME)

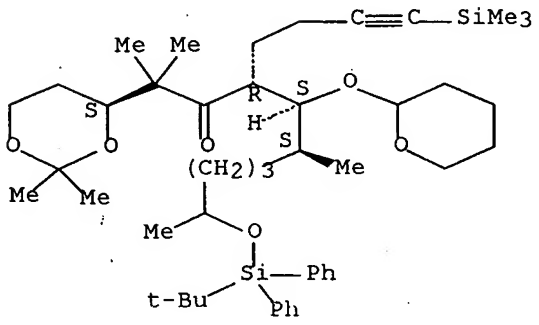
Absolute stereochemistry.



RN 364336-83-4 ZCAPLUS

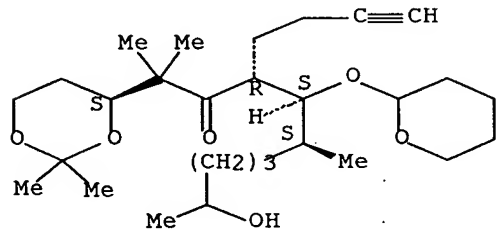
CN Dodecanoic acid, 3,7-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4,6,8-tetramethyl-5,12-dioxo-, methyl ester, (3S,6R,7S,8S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



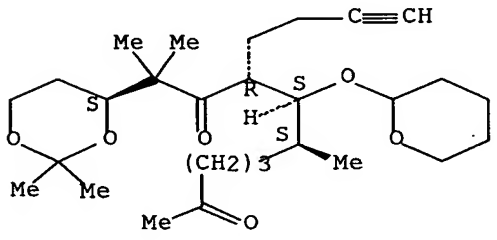
RN 303154-59-8 ZCAPLUS
CN 3-Undecanone, 4-(3-butynyl)-2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 303154-60-1 ZCAPLUS
CN 2,9-Undecanedione, 8-(3-butynyl)-10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L25 ANSWER 9 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:731069 ZCAPLUS Full-text
DOCUMENT NUMBER: 135:287591
TITLE: Preparation of epothilone intermediates
INVENTOR(S): Vite, Gregory D.; Kim, Soong-Hoon; Hoeefle, Gerhard

303154-59-8P 303154-60-1P

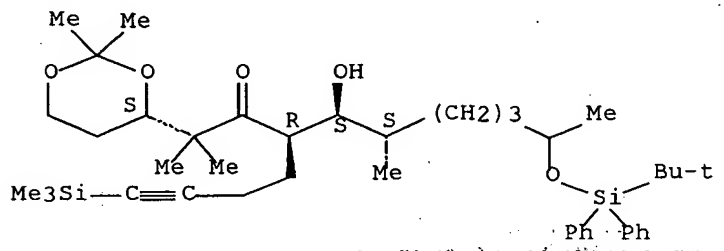
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 12,13-cyclopropylepothilone derivs. and their use in pharmaceutical compns.)

RN 303154-56-5 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

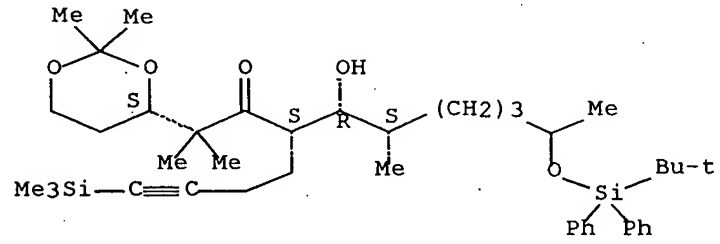
Absolute stereochemistry.



RN 303154-57-6 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 303154-58-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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FILE BEILSTEIN
FILE LAST UPDATED ON September 26, 2007

FILE COVERS 1771 TO 2007.
 FILE CONTAINS 10.119,480  SUBSTANCES

>>>PLEASE NOTE: Reaction Data and substance data are stored in
   separate documents and can not be searched together in one query.
   Reaction data for BEILSTEIN compounds may be displayed
   immediately with the display codes PRE (preparations) and REA
   (reactions).  A substance answer set retrieved after the search
   for a chemical name, a compounds with available reaction
   information by combining with PRE/FA, REA/FA or more generally
   with RX/FA. The BEILSTEIN Registry Number (BRN) is the link
   between a BEILSTEIN compound and belonging reactions. For mo
   detailed reaction searches BRNs can be searched as reaction
   partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE  <<<

*************************************************************
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST.       *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE  *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE         *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS.                       *
* FOR PRICE INFORMATION SEE HELP COST                               *
*************************************************************
    NEW
* PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE
  SEARCHED, SELECTED AND TRANSFERRED.
* NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES,
  ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A
  COMPOUND AT A GLANCE.

FILE BABS
FILE LAST UPDATED:          25 JUN 2007      <20070625/UP>
FILE COVERS 1980 TO DATE.

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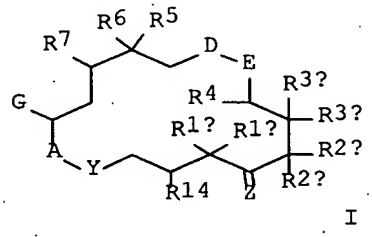
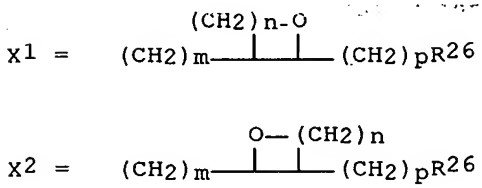
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10041470	A1	20020228	DE 2000-10041470	20000818
PRIORITY APPLN. INFO.:			DE 2000-10041470	20000818
OTHER SOURCE(S):	CASREACT 136:216592; MARPAT 136:216592			

GI

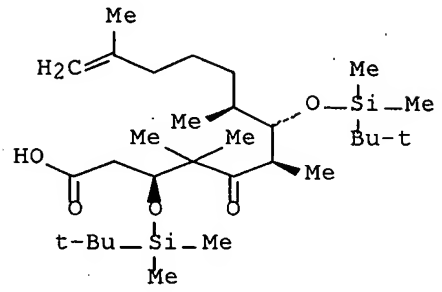


I



AB The present invention describes new 6-alkenyl- and 6-alkynylepothilone derivs., e.g., I [R1a, R1b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R1aR1b = (CH2)r, CH2OCH2; r = 1 - 5; R2a = H, C1-10-alkyl, aryl, C7-20-aralkyl, (CH2)m-C.tplbond.C-(CH2)pR26, (CH2)m-C:C-(CH2)pR26, X1, X2; n = 0 - 5; p = 0 - 3; m = 0 - 4; R2b = (CH2)m-C.tplbond.C-(CH2)pR26, (CH2)m-C:C- (CH2)pR26, X1, X2; R3a = H, C1-10-alkyl, aryl, C7-20-aralkyl; R3b = O-protecting group; R4 = H, C1-10-alkyl, aryl, C7-20-aralkyl, halogen, OH, O-protecting group, CN; R5 = H, C1-10-alkyl, aryl, C7-20-aralkyl, (CH2)s-T; S = 1 - 4; T = OH, O-protecting group, halogen; R6R7 = C(R33)2, NR32 AY = OC(:O), OCH2, CH2C(:O), NR29C(:O), NR29SO2; DE = CH2CH2, CH2O, OCH2; G = X:CR8-, bicyclic or tricyclic aryl; X = O, (O-alkyl)2, etc.; Z = H, H,OH, H,O-protective group; R8 = H, halogen, CN, C1-20-alkyl, aryl, C7-20-aralkyl; R14 = H, OH, halogen, O-SO2-alkyl, O-SO2-aryl, O-SO2-aralkyl; R26 = H, C1-10-alkyl, aryl, C7-20-aralkyl, C1-10-acyl, OH, O-protecting group; R29 = H, C1-20-alkyl; R32 = H, C1-4-alkyl, C1-4-acyl; R33 = H, halogen], which interact with tubulins by stabilizing the formed microtubulins (no data). I are able specifically to affect cell division and are suitable, for example for the treatment of malignant tumors ovarial -, stomach -, colon -, adeno -, chest -, lungs -, head and neck carcinoma, malignant melanoma, acute lymphocytic and myelocytic leukemia. In addition I are suitable for the anti-angiogenesis therapy as well as for the treatment of chronic ignitable illnesses (psoriasis, arthritis). For the avoidance of uncontrolled cell rampant growths on as well as the better compatibility of medical implants I can be up and/or brought into polymers materials. According to invention, I can be used alone or for the achievement of additive or synergistic effects in combination with further principles and substance classes applicable in the tumor therapy. Exptl. data from patents PCT/EP00/01333 and PCT/IB00/00657 are reproduced here.

IT ***303154-56-5P 303154-57-6P 303154-58-7P***



I

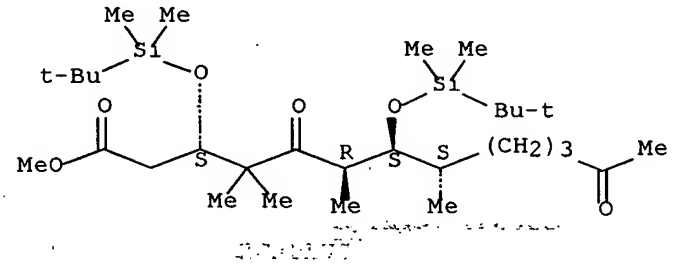
AB A facile and efficient route to epothilone analogs has been developed from the natural product epothilone D (I). Degradation of I via an oxidative cleavage sequence provides acid intermediate II rapidly in six steps. From II, a variety of epothilone analogs have been prepared utilizing ring-closing metathesis to reconstruct the trisubstituted-12,13-double bond. Using this approach, we report a number of epothilone analogs with varying C-15 aromatic side chains and C-14 allylic substitutions and their antitumor activities.

IT ***681259-79-0P***
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of epothilone D analogs via semisynthetic degradation and ring-closing metathesis and their antitumor activity)

RN 681259-79-0 ZCAPLUS

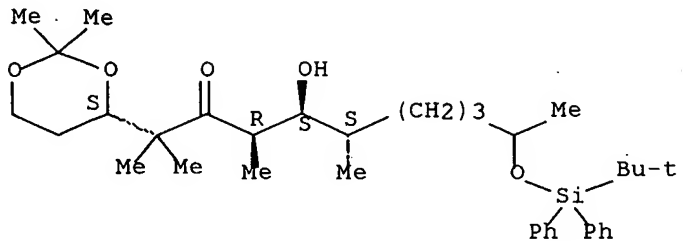
CN Tridecanoic acid, 3,7-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4,6,8-tetramethyl-5,12-dioxo-, methyl ester, (3S,6R,7S,8S)- (CA INDEX NAME)

Absolute stereochemistry.



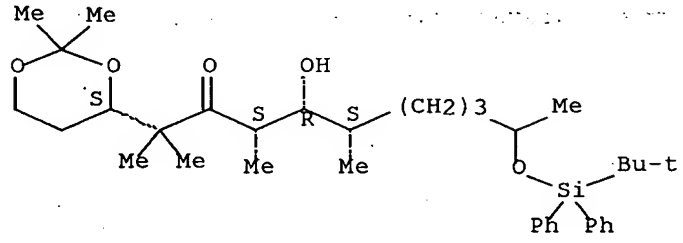
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 8 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:157050 ZCAPLUS Full-text
DOCUMENT NUMBER: 136:216592
TITLE: Procedures for the production of 12,13-cyclopropylepothilone derivatives, as well as for their use in pharmaceutical preparations
PATENT ASSIGNEE(S): Schering Ag, Germany
SOURCE: Ger. Offen., 64 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:



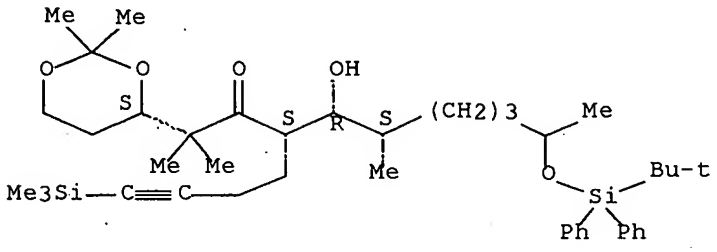
RN 823203-24-3 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,4,6-trimethyl-, (4S,5R,6S)-(CA INDEX NAME)

Absolute stereochemistry.



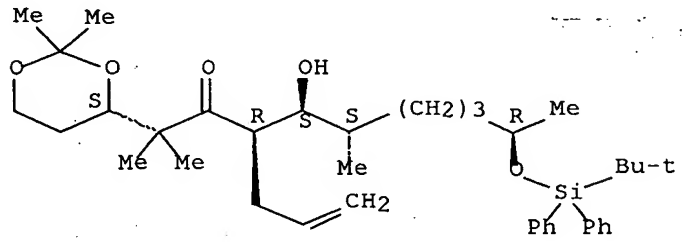
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 7 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:106102 ZCAPLUS Full-text
DOCUMENT NUMBER: 140:357084
TITLE: Rapid access to epothilone analogs via semisynthetic degradation and reconstruction of epothilone D
AUTHOR(S): Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C.
CORPORATE SOURCE: Department of Chemistry, Kosan Biosciences, Hayward, CA, 94545, USA
SOURCE: Tetrahedron Letters (2004), 45(9), 1945-1947
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:357084
GI



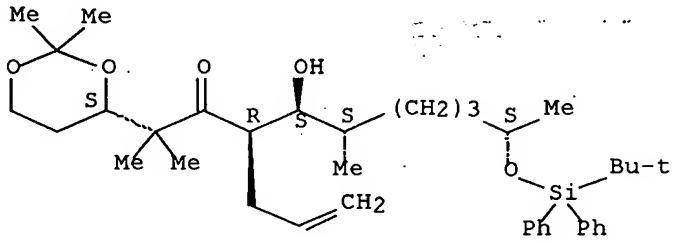
RN 823203-04-9 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(2-propenyl)-, (4R,5S,6S,10R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



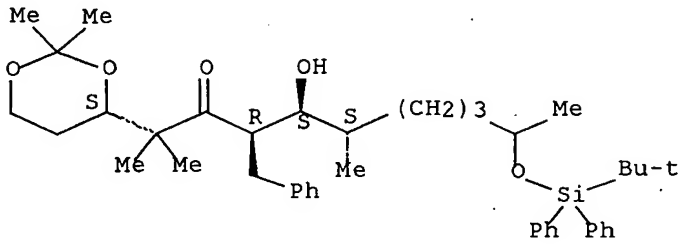
RN 823203-05-0 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(2-propenyl)-, (4R,5S,6S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



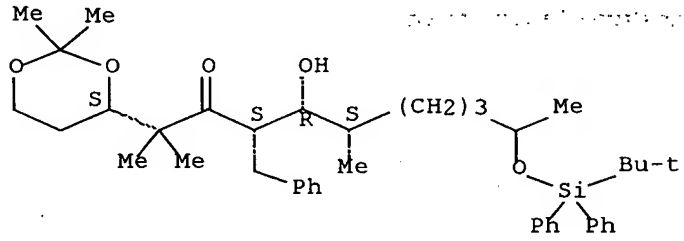
RN 823203-23-2 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,4,6-trimethyl-, (4R,5S,6S)- (CA INDEX NAME)

Absolute stereochemistry.



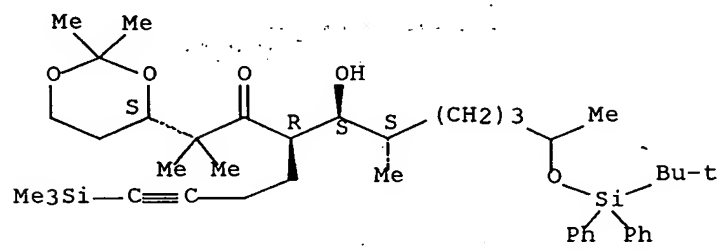
RN 220774-59-4 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(phenylmethyl)-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 303154-56-5 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



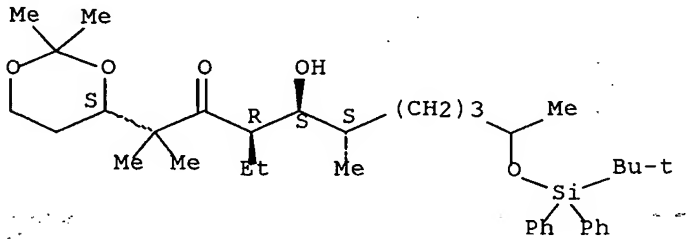
RN 303154-57-6 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

823203-04-9P 823203-05-0P 823203-23-2P
823203-24-3P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and tetrahydropyranylation of; method for producing C1-C15 fragments of epothilones and derivs. thereof)

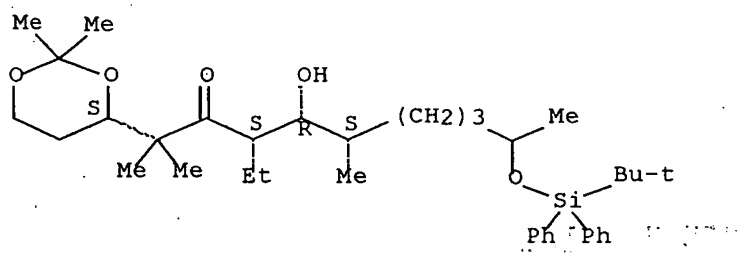
RN 220774-19-6 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



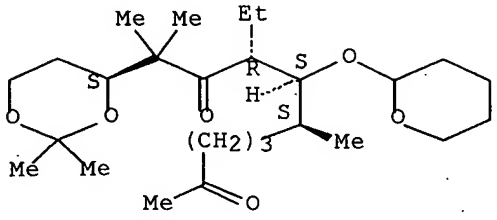
RN 220774-20-9 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



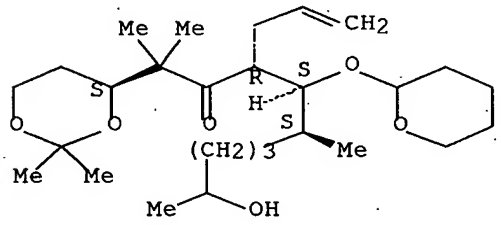
RN 220774-58-3 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(phenylmethyl)-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



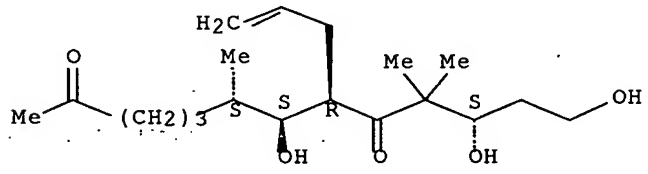
IT ***823203-07-2P***
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and perruthenate oxidation of; method for producing C1-C15 fragments of epothilones and derivs. thereof)
RN 823203-07-2 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-4-(2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT ***823203-19-6P***
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and silylation of; method for producing C1-C15 fragments of epothilones and derivs. thereof)
RN 823203-19-6 ZCAPLUS
CN 2,9-Tridecanedione, 7,11,13-trihydroxy-6,10,10-trimethyl-8-(2-propenyl)-, (6S,7S,8R,11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



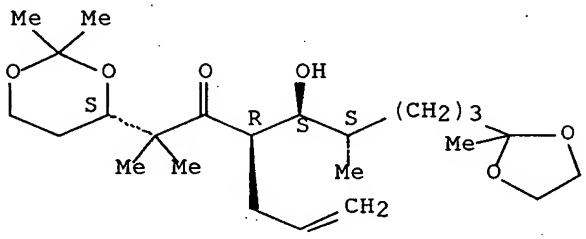
IT ***220774-19-6P 220774-20-9P 220774-58-3P***
220774-59-4P 303154-56-5P 303154-57-6P

preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and detetrahydropyranylation of; method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 823203-17-4 ZCAPLUS

CN 3-Nonanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-5-hydroxy-2,6-dimethyl-9-(2-methyl-1,3-dioxolan-2-yl)-4-(2-propenyl)-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

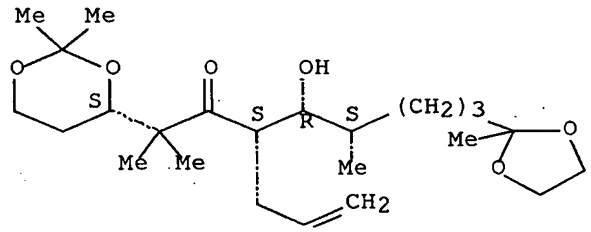
Absolute stereochemistry.



RN 823203-18-5 ZCAPLUS

CN 3-Nonanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-5-hydroxy-2,6-dimethyl-9-(2-methyl-1,3-dioxolan-2-yl)-4-(2-propenyl)-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



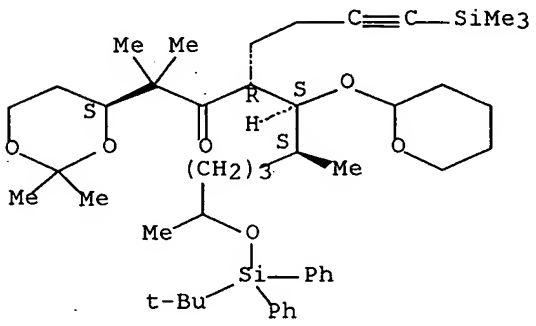
IT ***220774-23-2P***

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and detrahydropyranylation/deketalization of; method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 220774-23-2 ZCAPLUS

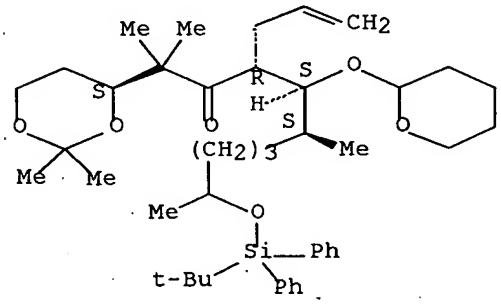
CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-8-ethyl-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



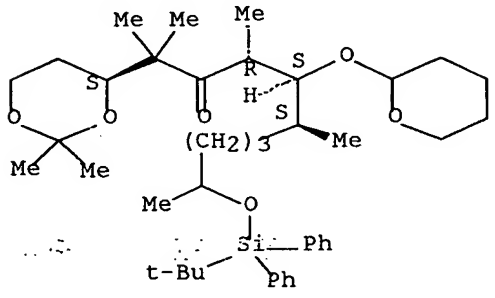
RN 823203-06-1 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-4-(2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 823203-25-4 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,4,6-trimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (CA INDEX NAME)

Absolute stereochemistry.

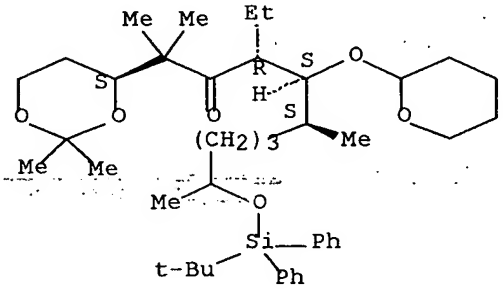


IT ***823203-17-4P 823203-18-5P***
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic

IT ***220774-21-0P 220774-60-7P 303154-58-7P 823203-06-1P 823203-25-4P***
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and desilylation of; method for producing C1-C15 fragments of epothilones and derivs. thereof)

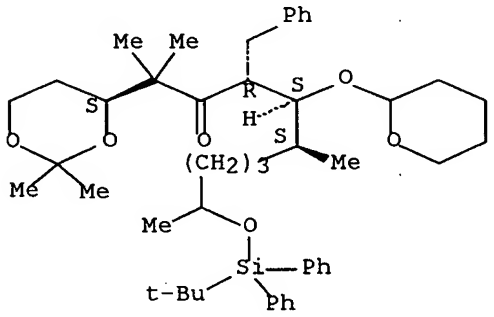
RN 220774-21-0 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 220774-60-7 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-4-(phenylmethyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

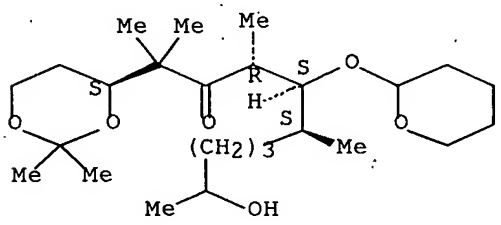


RN 303154-58-7 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

trimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (CA INDEX NAME)

Absolute stereochemistry.

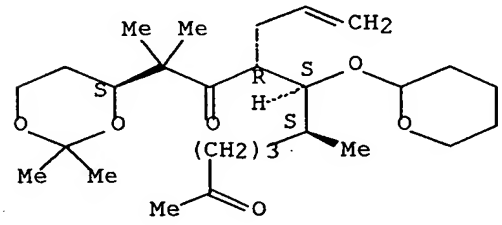


IT ***823203-08-3P 823203-20-9P***
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and Wittig reaction of, with (benzothiazolylpropyl)phosphonium iodide derivative; method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 823203-08-3 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-8-(2-propenyl)-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

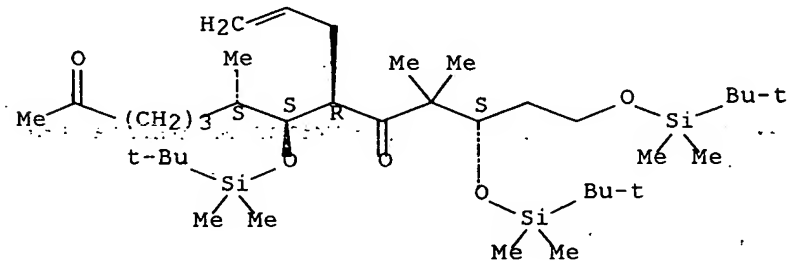
Absolute stereochemistry.



RN 823203-20-9 ZCAPLUS

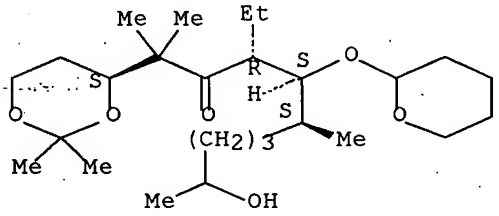
CN 2,9-Tridecanedione, 7,11,13-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6,10,10-trimethyl-8-(2-propenyl)-, (6S,7S,8R,11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



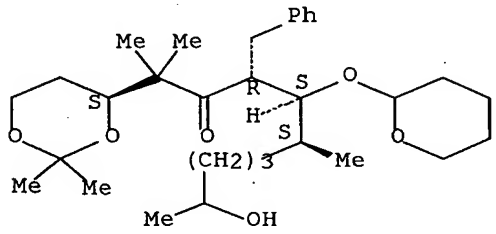
RN 220774-22-1 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-4-ethyl-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



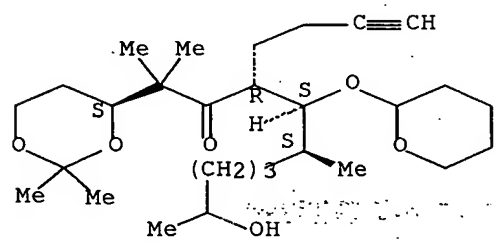
RN 220774-61-8 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-4-(phenylmethyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 303154-59-8 ZCAPLUS
CN 3-Undecanone, 4-(3-butynyl)-2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

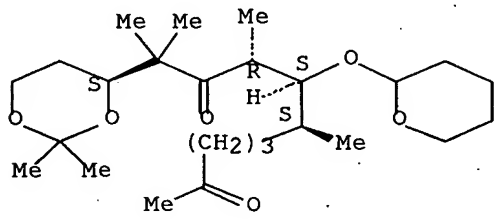
Absolute stereochemistry.



RN 823203-27-6 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,4,6-

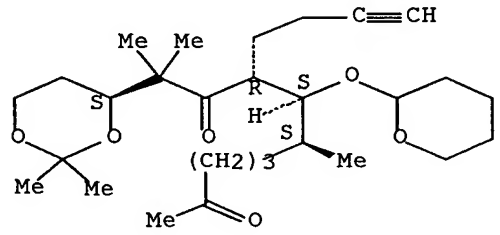
RN 220775-76-8 ZCAPLUS
CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,8,10-trimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



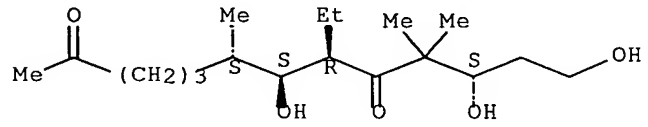
RN 303154-60-1 ZCAPLUS
CN 2,9-Undecanedione, 8-(3-butynyl)-10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 823203-02-7 ZCAPLUS
CN 2,9-Tridecanedione, 8-ethyl-7,11,13-trihydroxy-6,10,10-trimethyl-, (6S,7S,8R,11S)- (CA INDEX NAME)

Absolute stereochemistry.



IT ***220774-22-1P 220774-61-8P 303154-59-8P 823203-27-6P***
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and Swern oxidation of; method for producing C1-C15 fragments of epothilones and derivs. thereof)

alkyl, aryl, C7-20-aralkyl; R6, R7 = H; R6R7 = bond, O; G = X:CR8, bi- or tricyclic aryl; R8 = H, halogen, (un)substituted C1-20-alkyl, aryl, C7-20-aralkyl; X = O, (OR23)2, C2-10-alkylene- α,ω-dioxy, H(OR9), CR10R11; R23 = C1-20-alkyl; R9 = H, protecting group; R10, R11 = H, C1-10-alkyl, aryl, C7-20-aralkyl; CR10R11 = 5 - to 7-membered carbocycle; R13 = CH2OR13a, CH2-halo, CHO, CO2R13b, CO-halo; R13a, R14a = H, SO2alkyl, SO2-aryl, SO2-aralkyl; R13aR14a = (CH2)o, CR15aR15b; o = 2 - 4; R13b, R14b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R15a, R15b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R15aR15b = (CH2)q; q = 3 - 6; R20 = O-PG, NHR29, N3; Z = O, H(OR12); R12 = H, PG] of epothilones and derivs. The procedure comprises the bonding of a C1-C6 fragment, R13CH2CHR14CR1aR1bC(:O)CHR2aR2b, to a C7-C12 fragment, R5C(:V)(CH2)3CR4aR4bC(:W)R3a [V, W = O, (OR23)2, C2-10-alkylene- α,ω-dioxy, H(OR9)], to form a C1-C12 fragment, R5C(:V)(CH2)3CR4aR4bCR3a(O-PG14)CR2aR2bC(:Z)CR1aR1bCHR14CH2R13 [PG = H, protecting group], which is then treated with a C13-C15 fragment, G-CR20'CH2CHR7'R21 [R7' = H; R20' = halogen, N3, NHR29, OH, O-PG, NR29-PG, C1-20-(perfluoro)alkylsulfonyloxy, (C1-4-alkyl, NO2, Cl, Br-substituted) benzyloxy, NR29SO2Me, NR29C(:O)Me, CH2C(:O)Me; R21 = OH, halo, O-PG, P+Ph3Hal- (Hal = F, Cl, Br, I), P(O)(OQ)2 (Q = C1-10-alkyl, Ph), P(:O)Ph2; R29 = H, C1-6-alkyl], to form the C1-C15 epothilone intermediate product I. Thus, I [R1a = R1b = R5 = Me, R2a = CH2CH:CH2-β, R2b = R4b = H-α, R3 = H-β, R4a = Me-β, R6R7 = bond, R13 = CO2H, R14 = OSiMe2CMe3-β, R20 = OSiMe2CMe3-α, G = 2-methylbenzothiazol-5- yl, PG = SiMe2CMe3, Z = O] was prepared from (S)-4-(2-methyl-3-oxohept-6-en- 2-yl)-2,2-dimethyl-1,3-dioxane via lithiation and reaction with (2S,6RS)-2-methyl-6-[(tert-butyldimethylsilyl)oxy]heptanal, tetrahydropyranylation, desilylation with Bu4NF in THF, oxidation in CH2Cl2 containing N-methylmorpholine N-oxide and catalytic tetrapropylammonium perruthenate, Wittig reaction with [(3S)-3-(2-methylbenzothiazol-5- yl)propyl]triphenylphosphonium iodide, deisopropylidenation/detetrahydropy ranylation with catalytic 4-MeC6H4SO3H in EtOH, silylation with CF3SO2SiMe2CMe3, regioselective desilylation with (±)-camphor-10- sulfonic acid, Swern oxidation with DMSO/(COCl)2 in CH2Cl2 and carbonyl oxidation with NaOCl2 in aqueous THF/Me3COH. The produced C1-C15 epothilone intermediate products can be converted into the intrinsically active ingredients II [AK = OC(:O), OCH2, CH2C(:O), NR29C(:O), NR29SO2; R29 = H, C1-6-alkyl] according to known methods. The invention also relates to the corresponding C1-C12 fragments.

IT ***220774-62-9P 220775-76-8P 303154-60-1P 823203-02-7P***

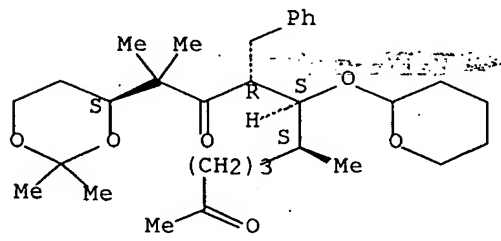
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 220774-62-9 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-8-(phenylmethyl)-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

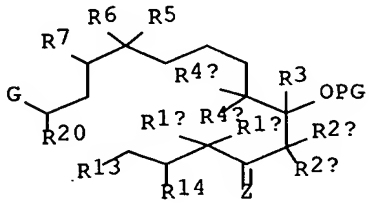


Skubalia, Werner
PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005003071	A1	20050113	WO 2004-EP6685	20040619
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10331004	A1	20050224	DE 2003-10331004	20030703
AU 2004254200	A1	20050113	AU 2004-254200	20040619
CA 2531078	A1	20050113	CA 2004-2531078	20040619
EP 1641734	A1	20060405	EP 2004-740122	20040619
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
CN 1816514	A	20060809	CN 2004-80019005	20040619
BR 2004012179	A	20060822	BR 2004-12179	20040619
IN 2006DN00056	A	20070824	IN 2006-DN56	20060103
MX 2006PA00172	A	20060427	MX 2006-PA172	20060105
NO 2006000554	A	20060403	NO 2006-554	20060202
US 2007142675	A1	20070621	US 2006-563058	20060619

PRIORITY APPLN. INFO.: DE 2003-10331004 A 20030703
WO 2004-EP6685 W 20040619

OTHER SOURCE(S): CASREACT 142:113814; MARPAT 142:113814
GI



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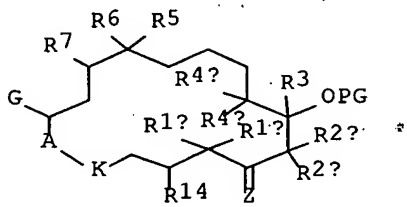


II

AB The invention relates to a method for preparing C1-C15 fragments I [R1a, R1b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R1aR1b = (CH2)m; m = 2 - 5; R2a, R2b = H, C1-10-alkyl, C2-10-alkenyl, C2-10-alkynyl, aryl, C7-20-aralkyl; R2aR2b = (CH2)n; n = 2 - 5; R3 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4a, R4b = = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4aR4b = (CH2)p; p = 2 - 5; R5 = H, C1-10-

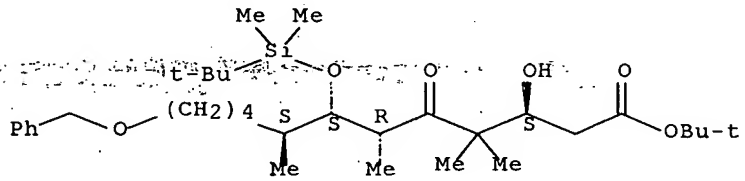
AB Synthesis of C1-C12 segment of epothilones A and B was achieved via diastereo- and regioselective opening of a trisubstituted epoxy ketone at the more substituted carbon. Epoxide I (R = SiMe2CMe3, R1 = benzyl) was cleaved selectively at the more substituted carbon using SmI2 in MeOH/THF at -90° to form the silyl protected β-hydroxyketone II which contains the C5-C7 epothilone aldol moiety.

IT ***201683-59-2P***
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of C1-C12 segment of epothilones A and B via radical induced opening of trisubstituted epoxides)

RN 201683-59-2 ZCAPLUS

CN Dodecanoic acid, 7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-hydroxy-4,4,6,8-tetramethyl-5-oxo-12-(phenylmethoxy)-, 1,1-dimethylethyl ester, [3S-(3R*,6S*,7R*,8R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

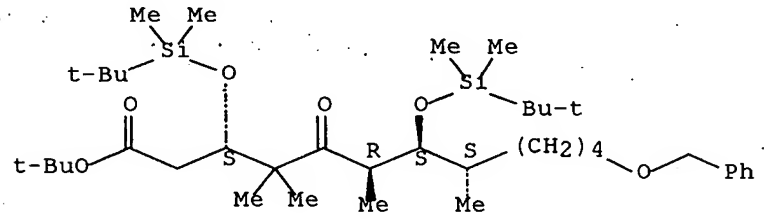


IT ***201683-49-0P***
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of C1-C12 segment of epothilones A and B via radical induced opening of trisubstituted epoxides)

RN 201683-49-0 ZCAPLUS

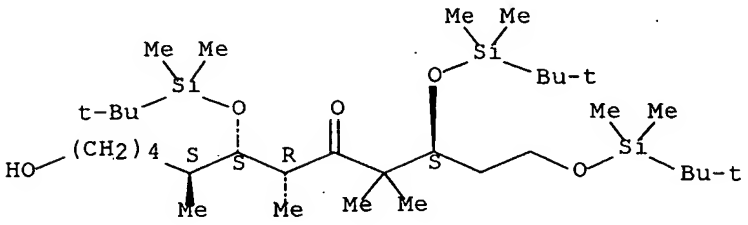
CN Dodecanoic acid, 3,7-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4,6,8-tetramethyl-5-oxo-12-(phenylmethoxy)-, 1,1-dimethylethyl ester, [3S-(3R*,6S*,7R*,8R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



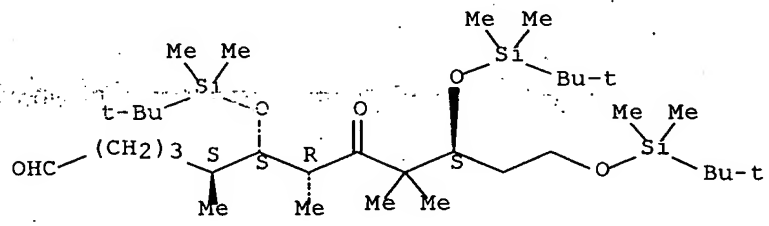
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 6 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:29293 ZCAPLUS Full-text
DOCUMENT NUMBER: 142:113814
TITLE: Method for producing C1-C15 fragments of epothilones and derivatives thereof
INVENTOR(S): Klar, Ulrich; Buchmann, Bernd; Schwede, Wolfgang;



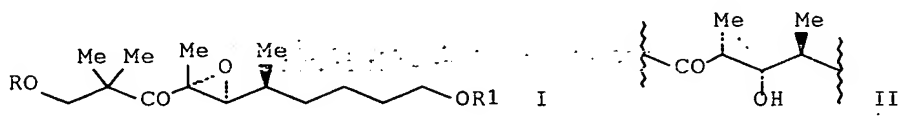
RN 346652-91-3 ZCAPLUS
CN Dodecanal, 6,10,12-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,7,9,9-tetramethyl-8-oxo-, (5S,6S,7R,10S)- (9CI) (CA INDEX NAME)

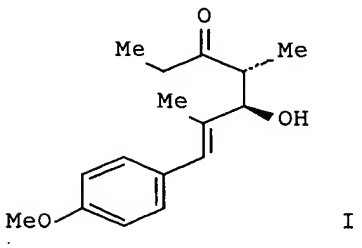
Absolute stereochemistry.



REFERENCE COUNT: 117 THERE ARE 117 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 5 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 1998:14400 ZCAPLUS Full-text
DOCUMENT NUMBER: 128:114806
TITLE: Radical-induced opening of trisubstituted epoxides: application in the synthesis of C1-C12 segment of epothilones
AUTHOR(S): Chakraborty, T. K.; Dutta, S.
CORPORATE SOURCE: Indian Inst. Chem. Technol., Hyderabad, 500 007, India
SOURCE: Tetrahedron Letters (1998), 39(1/2), 101-104
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 128:114806
GI





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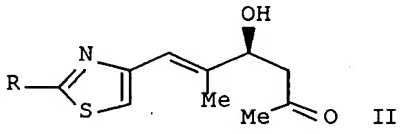


II

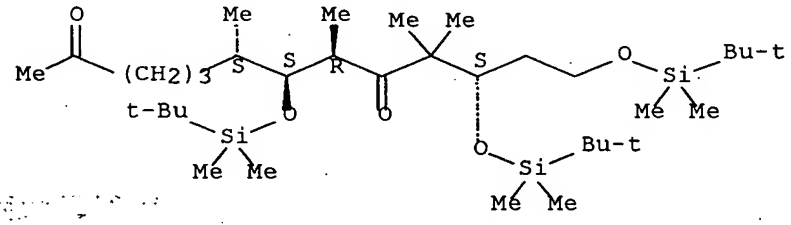
AB Naturally occurring epothilones have been synthesized starting from enantiomerically pure aldol compds. I and II, which were obtained by antibody catalysis. Aldolase antibody 38C2 catalyzed the resolution of (±)-I by enantioselective retro-aldol reaction to afford I in 90% ee at 50% conversion. Compds. II (R = Me, CH2OH) were obtained in more than 99% ee at 50% conversion by resolution of their racemic mixts. using newly developed aldolase antibodies 84G3, 85H6 or 93F3. Compds. I and II were resolved in multigram quantities and then converted to the epothilones by metathesis processes, which were catalyzed by Grubbs' catalysts.

IT ***346651-96-5P***
RL: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of epothilones A-F)

RN 346651-96-5 ZCAPLUS

CN 2,9-Tridecanedione, 7,11,13-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6,8,10,10-tetramethyl-, (6S,7S,8R,11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT ***346652-88-8P 346652-91-3P***
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of epothilones A-F)

RN 346652-88-8 ZCAPLUS

CN 4,12-Dioxa-3,13-disilapentadecan-7-one, 9-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[(1S)-5-hydroxy-1-methylpentyl]-2,2,3,3,6,8,8,13,13,14,14-undecamethyl-, (5S,6R,9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

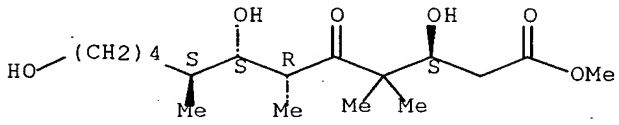
CORPORATE SOURCE: Abteilung Naturstoffchemie, Gesellschaft fuer Biotechnologische Forschung mbH, Braunschweig, D-38124, Germany
SOURCE: Journal of the Chemical Society, Perkin Transactions 1 (2002), (22), 2490-2503
CODEN: JCSPCE; ISSN: 1472-7781
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:187542

AB Novel and unique chiral building blocks of high structural diversity were obtained by selective chemical fragmentation of natural products from myxobacteria. Subsequent modification reactions provided primary alc. and carboxylic acid derivs., which are suitable for the construction of combinatorial chemical libraries. The single SPOT synthesis of a hybrid structure on a polypropylene membrane was employed to demonstrate the chemical recombination of such rare building blocks on a micro-scale.

IT ***498580-02-2P***
RL: SPN (Synthetic preparation); PREP (Preparation)
(fragmentation of natural products from myxobacteria as building blocks for combinatorial synthesis)

RN 498580-02-2 ZCAPLUS
CN Dodecanoic acid, 3,7,12-trihydroxy-4,4,6,8-tetramethyl-5-oxo-, methyl ester, (3S,6R,7S,8S)- (CA INDEX NAME)

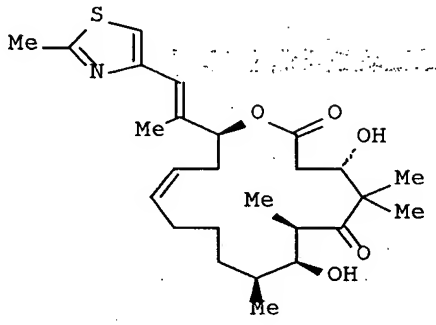
Absolute stereochemistry.



REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 4 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2001:316603 ZCAPLUS Full-text
DOCUMENT NUMBER: 135:76707
TITLE: Catalytic antibody route to the naturally occurring epothilones: total synthesis of epothilones A - F
AUTHOR(S): Sinha, Subhash C.; Sun, Jian; Miller, Gregory P.; Wartmann, Markus; Lerner, Richard A.
CORPORATE SOURCE: Department of Molecular Biology and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Chemistry--A European Journal (2001), 7(8), 1691-1702
CODEN: CEUJED; ISSN: 0947-6539
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:76707
GI

CODEN: ACIEF5; ISSN: 1433-7851
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:197285
GI



I

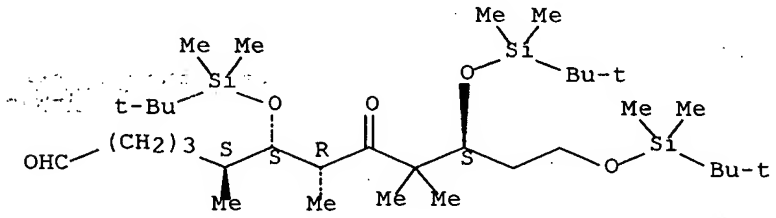
AB A total synthesis of epothilone C (I) with concomitant formal synthesis of epothilone A is described, using immobilized reagents and scavengers to effect multistep synthetic transformations and purifications.

IT ***346652-91-3P***
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of epothilones using solid-supported reagents and scavengers)

RN 346652-91-3 ZCAPLUS

CN Dodecanal, 6,10,12-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,7,9,9-tetramethyl-8-oxo-, (5S,6S,7R,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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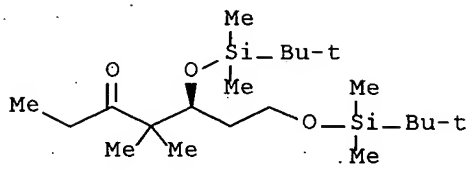
L25 ANSWER 3 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2002:863402 ZCAPLUS Full-text
DOCUMENT NUMBER: 138:187542
TITLE: Natural product-derived building blocks for combinatorial synthesis. Part 1. Fragmentation of natural products from myxobacteria
AUTHOR(S): Niggemann, Jutta; Michaelis, Katrin; Frank, Ronald; Zander, Norbert; Hoefle, Gerhard



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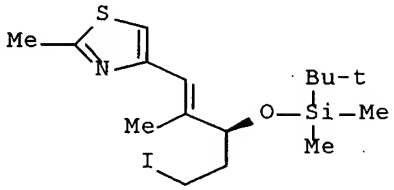


II

AB The total synthesis of the cytotoxic antitumor natural product epothilone C has provided a stage for the exploitation and further development of immobilized reagent methods. A stereoselective convergent synthetic strategy was applied, incorporating polymer-supported reagents, catalysts, scavengers and catch-and-release techniques to avoid frequent aqueous work-up and chromatog. purification The enantioselective preparation of 3 key fragments heptanone I, (S)-2-methyl-6-heptenal, and thiazole II along with their elaboration via diastereoselective coupling into epothilone C is presented.

IT ***346652-91-3P***

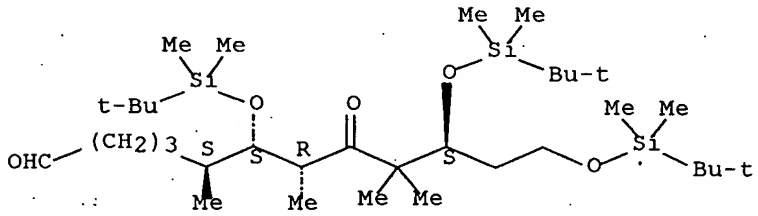
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of epothilone C via asym. synthesis and stereoselective coupling of heptanone, methylheptenal, and thiazole fragments using immobilized reagents and scavengers)

RN 346652-91-3 ZCAPLUS

CN Dodecanal, 6,10,12-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,7,9,9-tetramethyl-8-oxo-, (5S,6S,7R,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 2 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 2

ACCESSION NUMBER: 2003:494861 ZCAPLUS Full-text

DOCUMENT NUMBER: 139:197285

TITLE: A total synthesis of epothilones using solid-supported reagents and scavengers

AUTHOR(S): Storer, R. Ian; Takemoto, Toshiyasu; Jackson, Philip S.; Ley, Steven V.

CORPORATE SOURCE: University Chemical Laboratories, University of Cambridge, Cambridge, CB2 1EW, UK

SOURCE: Angewandte Chemie, International Edition (2003), 42(22), 2521-2525

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FILE 'BABS' ENTERED AT 15:47:21 ON 11 OCT 2007
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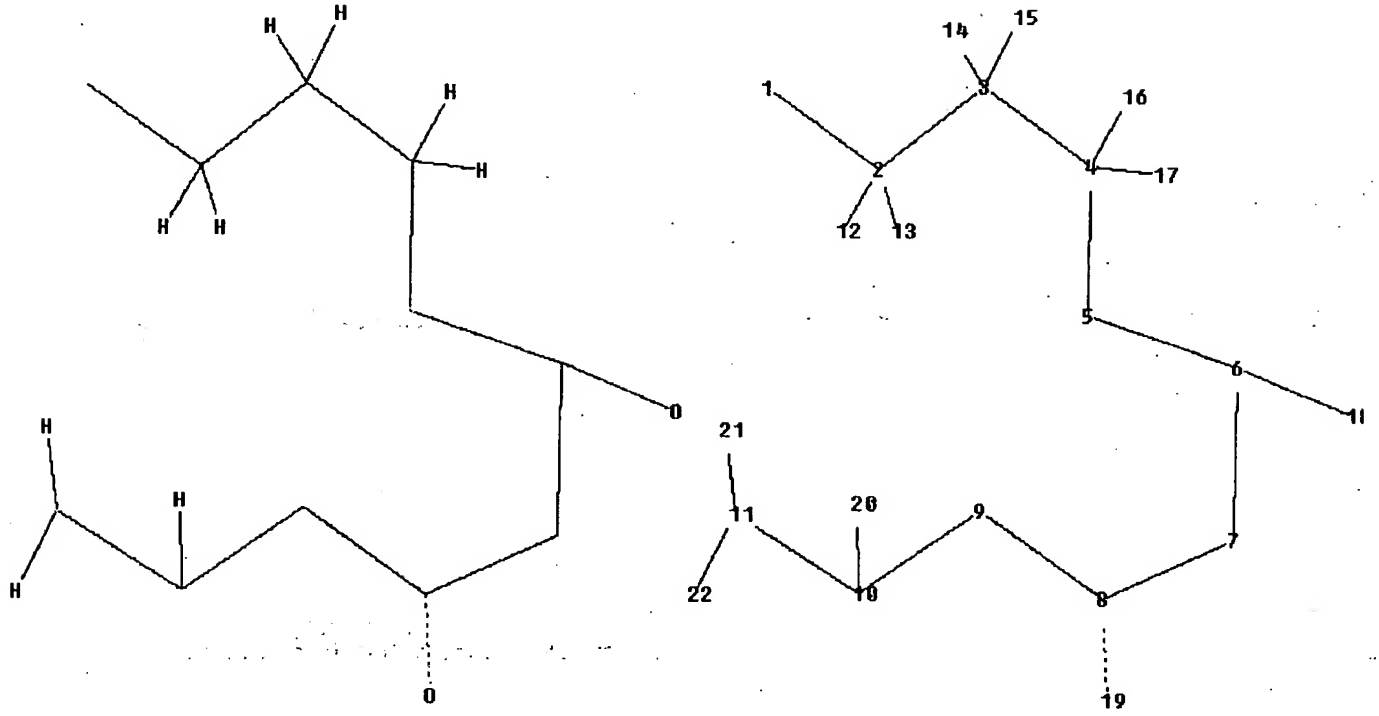
PROCESSING COMPLETED FOR L6
PROCESSING COMPLETED FOR L19
PROCESSING COMPLETED FOR L14
L25 25 DUP REM L6 L19 L14 (7 DUPLICATES REMOVED)
ANSWERS '1-18' FROM FILE ZCAPLUS
ANSWERS '19-25' FROM FILE BEILSTEIN

=> d ibib abs hitstr L25 1-18; d ide allref L25 19-25

L25 ANSWER 1 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:454851 ZCAPLUS Full-text
DOCUMENT NUMBER: 141:140221
TITLE: Multi-step application of immobilized reagents and scavengers: A total synthesis of epothilone C
AUTHOR(S): Storer, R. Ian; Takemoto, Toshiyasu; Jackson, Philip S.; Brown, Dearg S.; Baxendale, Ian R.; Ley, Steven V.
CORPORATE SOURCE: Department of Chemistry, University of Cambridge, Cambridge, CB2 1EW, UK
SOURCE: Chemistry--A European Journal (2004), 10(10), 2529-2547
CODEN: CEUJED; ISSN: 0947-6539
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:140221
GI

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12  13  14  15  16  17  18  19  20  21  22
ring/chain nodes :
1  2  3  4  5  6  7  8  9  10  11
chain bonds :
2-12  2-13  3-14  3-15  4-16  4-17  6-18  8-19  10-20  11-21  11-22
ring/chain bonds :
1-2  2-3  3-4  4-5  5-6  6-7  7-8  8-9  9-10  10-11
exact/norm bonds :
1-2  2-3  3-4  4-5  5-6  6-7  6-18  7-8  8-9  8-19  9-10  10-11
exact bonds :
2-12  2-13  3-14  3-15  4-16  4-17  10-20  11-21  11-22

Match level :
1:CLASS  2:CLASS  3:CLASS  4:CLASS  5:CLASS  6:CLASS  7:CLASS  8:CLASS  9:CLASS
10:CLASS  11:CLASS  12:CLASS  13:CLASS  14:CLASS  15:CLASS  16:CLASS  17:CLASS
18:CLASS  19:CLASS
20:CLASS  21:CLASS  22:CLASS


L3              SCR 1008
L11          38 SEA FILE=BEILSTEIN SSS FUL L1 AND L3
L12          26 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L11/COM
L13           5 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L12 AND BABSAN/FA
L15          21 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L12 NOT L13
L16          14 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L15 AND RN/FA
L19           7 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L15 NOT L16


=> file babs
FILE 'BABS' ENTERED AT 15:47:02 ON 11 OCT 2007
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FILE COVERS 1771 TO 2007.
*** FILE CONTAINS 10.119,480 SUBSTANCES ***

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For mo detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

```
**********************************************************************
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST.                *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE   *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE          *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS.                        *
* FOR PRICE INFORMATION SEE HELP COST                                *
**********************************************************************
```

NEW

* ***PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.***
* ***NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.***

```
=> d stat que L19
L1              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation:
Uploading L1.str
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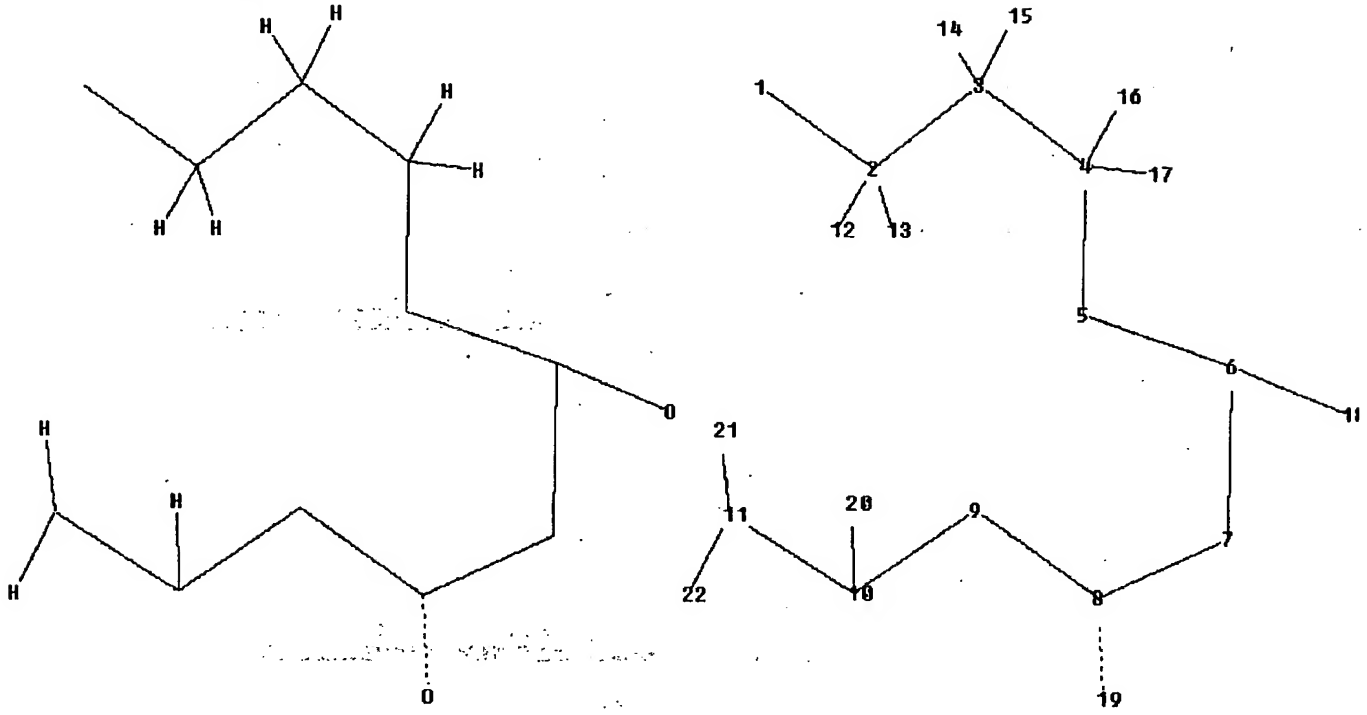

chain nodes :
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ring/chain nodes :
1 2 3 4 5 6 7 8 9 10 11
chain bonds :
2-12 2-13 3-14 3-15 4-16 4-17 6-18 8-19 10-20 11-21 11-22
ring/chain bonds :
1-2 2-3 3-4 4-5 5-6 6-7 7-8 8-9 9-10 10-11
exact/norm bonds :
1-2 2-3 3-4 4-5 5-6 6-7 6-18 7-8 8-9 8-19 9-10 10-11
exact bonds :
2-12 2-13 3-14 3-15 4-16 4-17 10-20 11-21 11-22

Match level :
1:CLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS
10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS
18:CLASS 19:CLASS
20:CLASS 21:CLASS 22:CLASS

L3 SCR 1008
L5 68 SEA FILE=REGISTRY SSS FUL L1 AND L3
L6 18 SEA FILE=ZCAPLUS ABB=ON PLU=ON L5

=> file beilstein
FILE 'BEILSTEIN' ENTERED AT 15:46:51 ON 11 OCT 2007

FILE LAST UPDATED ON September 26, 2007

```
=> file registry
FILE 'REGISTRY' ENTERED AT 15:46:28 ON 11 OCT 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   10 OCT 2007  HIGHEST RN 950149-06-1
DICTIONARY FILE UPDATES:  10 OCT 2007  HIGHEST RN 950149-06-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> file zcaplus
FILE 'ZCAPLUS' ENTERED AT 15:46:31 ON 11 OCT 2007
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FILE COVERS 1907 - 11 Oct 2007  VOL 147 ISS 16
FILE LAST UPDATED: 10 Oct 2007  (20071010/ED)

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  This file contains CAS Registry Numbers for easy and accurate
  substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'ZCAPLUS' FILE

=> d stat que L6
L1              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation:
Uploading L1.str
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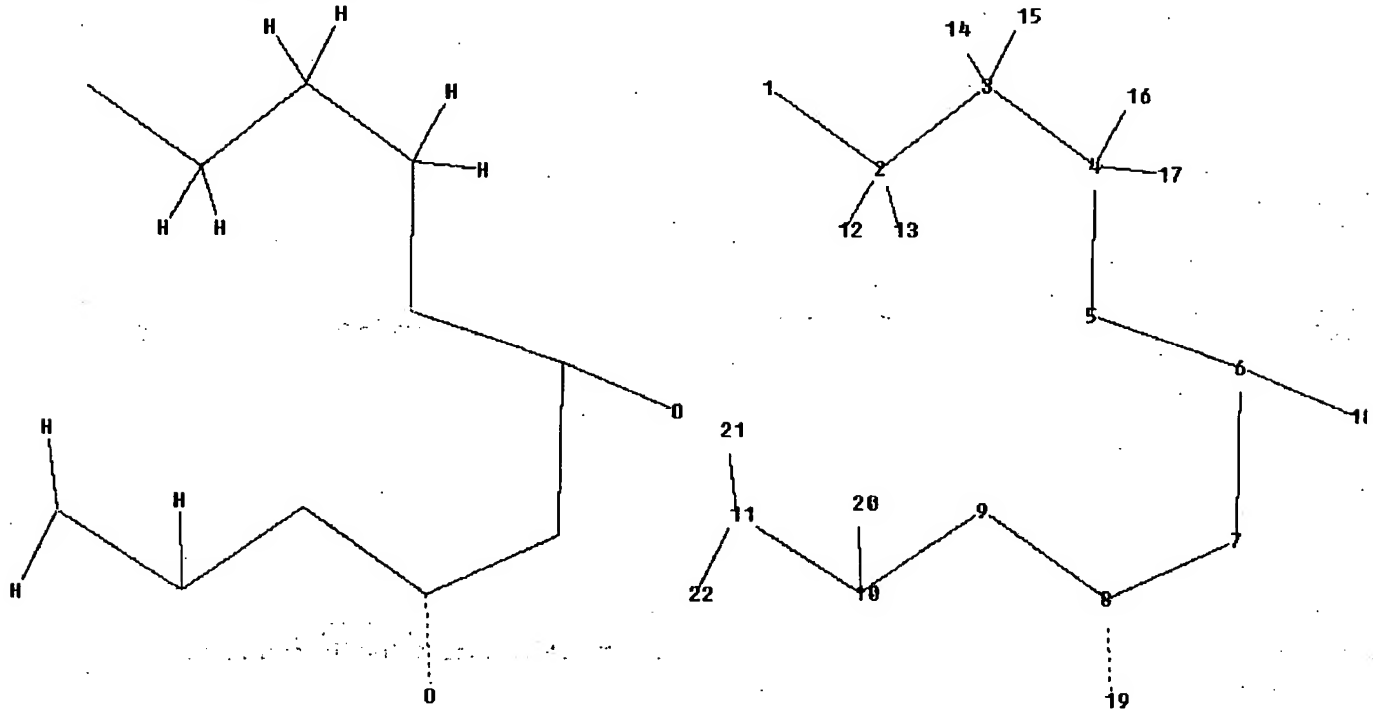

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chain nodes :
12  13  14  15  16  17  18  19  20  21  22
ring/chain nodes :
1  2  3  4  5  6  7  8  9  10  11
chain bonds :
2-12  2-13  3-14  3-15  4-16  4-17  6-18  8-19  10-20  11-21  11-22
ring/chain bonds :
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exact/norm bonds :
1-2  2-3  3-4  4-5  5-6  6-7  6-18  7-8  8-9  8-19  9-10  10-11
exact bonds :
2-12  2-13  3-14  3-15  4-16  4-17  10-20  11-21  11-22

Match level :
1:CLASS  2:CLASS  3:CLASS  4:CLASS  5:CLASS  6:CLASS  7:CLASS  8:CLASS  9:CLASS
10:CLASS  11:CLASS  12:CLASS  13:CLASS  14:CLASS  15:CLASS  16:CLASS  17:CLASS
18:CLASS  19:CLASS
20:CLASS  21:CLASS  22:CLASS


L3              SCR 1008
L11          38 SEA FILE=BEILSTEIN SSS FUL L1 AND L3
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L16          14 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L15 AND RN/FA
L19           7 SEA FILE=BEILSTEIN ABB=ON  PLU=ON  L15 NOT L16


=> file babs
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```

```
FILE COVERS 1771 TO 2007.
*** FILE CONTAINS 10.119,480  SUBSTANCES ***

>>>PLEASE NOTE: Reaction Data and substance data are stored in
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   Reaction data for BEILSTEIN compounds may be displayed
   immediately with the display codes PRE (preparations) and REA
   (reactions).  A substance answer set retrieved after the search
   for a chemical name, a compounds with available reaction
   information by combining with PRE/FA, REA/FA or more generally
   with RX/FA. The BEILSTEIN Registry Number (BRN) is the link
   between a BEILSTEIN compound and belonging reactions. For mo
   detailed reaction searches BRNs can be searched as reaction
   partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

**********************************************************************
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST.                 *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE    *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE           *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS.                         *
* FOR PRICE INFORMATION SEE HELP COST                                 *
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    NEW
* PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE
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  ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A
  COMPOUND AT A GLANCE.

=> d stat que L19
L1              STR

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Structure attributes must be viewed using STN Express query preparation:
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/006685

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C49/17 C07D417/06 C07D493/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/07692 A (KLAR ULRICH ; SCHERING AG (DE); BUCHMANN BERND (DE); SKUBALLA WERNER () 18 February 1999 (1999-02-18) cited in the application page 49, line 1 - page 50, line 15; claim 9	1-5

US 2003/0144523

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 October 2004	20/10/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Seelmann, I

Form PCT/ISA/210 (second sheet) (January 2004)

Abstract

This invention describes a process for the production of C_1-C_{15}-fragments of epothilones and derivatives thereof, in which a C1–C6-fragment is linked with a C7–C12-fragment to a C1–C12-fragment, and the latter then is reacted with a C13–C15-fragment to form the C1–C15 initial epothilone product that is to be produced.

The thus obtained C1–C15 initial epothilone products can be reacted according to known methods to form the actual active ingredients.

In addition, the invention relates to the corresponding C1–C12-fragments.

Translation

10/563058
LSR

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
53110AWO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/006685	19.06.2004	03.07.2003

International Patent Classification (IPC) or national classification and IPC

C07C49/17, C07D417/06, C07D493/04

Applicant

SCHERING AKTIENGESELLSCHAFT

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006685

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rule 12.3 and 23.1(b))

☐ publication of the international application (Rule 12.4)

☐ international preliminary examination (Rule 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:

pages 1-36 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

☒ the claims:

nos. 1-5 as originally filed/furnished

nos.* _____ as amended (together with any statement) under Article 19

nos.* _____ received by this Authority on _____

nos.* _____ received by this Authority on _____

☐ the drawings:

sheets _____ as originally filed/furnished

sheets* _____ received by this Authority on _____

sheets* _____ received by this Authority on _____

☐ a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/006685

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims		YES
	Claims	1-5	NO
Inventive step (IS)	Claims		YES
	Claims	1-5	NO
Industrial applicability (IA)	Claims	1-5	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The present application appears not to satisfy the requirements of PCT Article 33(2) because the subject matter of the claims is not novel. Claim 9 and pages 49-50 of the description of document D1 (WO 99/07692 A) concern, *inter alia*, a method for producing epothilone derivatives from the fragments A+B = A-B and A-B + C = A-B-C, wherein all three fragments structurally overlap the A, B and C claimed in the present application. The formula AB in claim 9 of document D1 therefore appears to be prejudicial to the novelty of the present claim 5. The method of claim 9 of document D1 likewise appears to be prejudicial to the novelty of present claims 1-4. In particular, in the C fragment U=C-R appears to overlap with G in document D1, and in fragment AB CH-CH versus D-E in AB of document D1 does not result in a new selection, since D-E form a unit, that is to say, they cannot be selected independently of each other. Consequently, this is considered no more than a selection from a list.

Document D1 is the closest prior art. It discloses the production of epothilone derivatives from the fragments A+B = A-B and A-B + C = A-B-C. The problem to be solved

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

by the present invention is understood to be that of providing an alternative method for producing epothilones. In the light of the experimental part it can be assumed that this problem is solved by the application. However, insofar as the subject matter of the present application can be considered novel, the fragments A, B and C are similar to those of document D1 to such an extent that the solution is obvious to a person skilled in the art. The problem to be solved by the present application must therefore be considered that of an alternative method having unexpected or surprising properties with respect to the closest prior art (D1). Without comparative test results or other arguments demonstrating the patentability of the invention it is not possible to assess whether the invention satisfies the requirements of PCT Article 33(3). The present application does not appear to meet the requirements of PCT Article 33(2) because the subject matter of the claims is not novel. Claim 9 and pages 49-50 of the description of document D1 (WO 99/07692 A) concern, *inter alia*, a method for producing epothilone derivatives from the fragments A+B = A-B and A-B + C = A-B-C, wherein all three fragments structurally overlap with the fragments A, B and C claimed in the present application. The formula AB in claim 9 of document D1 therefore appears to be prejudicial to the novelty of the present claim 5. The method of claim 9 of document D1 likewise appears to be prejudicial to the novelty of the present claims 1-4. In particular, in the C fragment, U=C-R appears to overlap with G in document D1, and in fragment AB, CH-CH as opposed to D-E in AB of document D1 does not lead to a novel selection, since D-E form a unit, that is to say,

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

they cannot be selected independently of each other. Consequently, this is considered no more than a selection from a list.

Document D1 is the closest prior art. It discloses the production of epothilone derivatives from the fragments A+B = A-B and A-B + C = A-B-C. The problem to be solved by the present invention is understood to be that of providing an alternative method for the production of epothilones. In the light of the experimental part, it can be assumed that this problem is solved in the application. However, insofar as the subject matter of the present application can be considered novel, the fragments A, B and C are similar to those of document D1 to such an extent that the solution is obvious to a person skilled in the art. The problem to be solved by the present application must therefore considered that of making available an alternative method having unexpected or surprising properties with respect to the closest prior art document (D1). Without comparative test results or other arguments demonstrating the patentability of the invention it is not possible to assess whether the invention satisfies the requirements of PCT Article 33(3).

Lao, MariaLouisa

From: DiNatale, John
Sent: Thursday, October 11, 2007 4:01 PM
To: Lao, MariaLouisa
Subject: 10/563058

Examiner Lao,

Your search results for serial number 10/563058 are complete and have been submitted to SCORE for posting. Routinely these results will be posted as early as tomorrow. Please see the instructions at the bottom of this email for retrieving search results from eDan 2.2.1.

****Search-specific notes:**

The search results are located in 2 RTF files.

The organization of the search results within the RTF file called 20071011-10563058-str1.rtf is sequential, divided by page breaks:
1) author search
2) Claim 1 reaction search,
3) Claim 4 reaction search,
and
4) search history.

The organization of the search results within the RTF file called 20071011-10563058-str2.rtf is sequential, divided by page breaks:
1) Claim 5 structure search
and
2) search history.

It may be helpful to save this memo as an index to the search results.

Please contact me if you have any questions.

Thank you,
John DiNatale
X2-2557

To access your search results via eDAN:

1) Enter Application number
2) Click on Supplemental Content Tab
3) STN results (structure and text searches) are under **Other Content** (click on version listed). ABSS Sequence results are under the **Search Results** (click on version listed).

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                -3/BI OR 220774-19-6/BI OR 220774-20-9/BI OR 220774-21-0/BI OR
                220774-22-1/BI OR 220774-23-2/BI OR 220774-57-2/BI OR 220774-58
                -3/BI OR 220774-59-4/BI OR 220774-60-7/BI OR 220774-61-8/BI OR
                220774-62-9/BI OR 220775-18-8/BI OR 220775-76-8/BI OR 289477-70
                -9/BI OR 289477-71-0/BI OR 289477-72-1/BI OR 289477-73-2/BI OR
                289477-74-3/BI OR 303154-55-4/BI OR 303154-56-5/BI OR 303154-57
                -6/BI OR 303154-58-7/BI OR 303154-59-8/BI OR 303154-60-1/BI OR
                305840-13-5/BI OR 823203-01-6/BI OR 823203-02-7/BI OR 823203-03
                -8/BI OR 823203-04-9/BI OR 823203-05-0/BI OR 823203-06-1/BI OR
                823203-07-2/BI OR 823203-08-3/BI OR 823203-09-4/BI OR 823203-10
                -7/BI OR 823203-11-8/BI OR 823203-12-9/BI OR 823203-13-0/BI OR
                823203-14-1/BI OR 823203-15-2/BI OR 823203-16-3/BI OR 823203-17
                -4/BI OR 823203-18-5/BI OR 823203-19-6/BI OR 823203-20-9/BI OR
                823203-23-2/BI OR 823203-24-3/BI OR 823203-25-4/BI OR 823203-27
                -6/BI)
L67           2 SEA ABB=ON  PLU=ON  L66 AND L39
                D SCA

    FILE 'CAPLUS' ENTERED AT 11:50:53 ON 11 OCT 2007
L68           1 SEA ABB=ON  PLU=ON  L67 AND L65
                D SCA

    FILE 'REGISTRY' ENTERED AT 11:54:40 ON 11 OCT 2007
                E EPOTHILONE C/CN
L69           1 SEA ABB=ON  PLU=ON  EPOTHILONE C/CN
                D SCA
L70           1 SEA ABB=ON  PLU=ON  EPOTHILONE D/CN
                D SCA
                D RN L67 1-2

    FILE 'CASREACT' ENTERED AT 11:56:56 ON 11 OCT 2007
L71          21 SEA ABB=ON  PLU=ON  152044-54-7/PRO
L72          14 SEA ABB=ON  PLU=ON  152044-53-6/PRO
L73           7 SEA ABB=ON  PLU=ON  L42 (L) L71
L74           7 SEA ABB=ON  PLU=ON  L42 (L) L72
L75          14 SEA ABB=ON  PLU=ON  (L73 OR L74)
L76          13 SEA ABB=ON  PLU=ON  L75 NOT L60

    FILE 'CAPLUS' ENTERED AT 11:58:45 ON 11 OCT 2007
L77          11 SEA ABB=ON  PLU=ON  L45 AND PY<2000
                SEL AN

    FILE 'CASREACT' ENTERED AT 12:00:01 ON 11 OCT 2007
L78          11 SEA ABB=ON  PLU=ON  ("126:251010"/AN OR "127:108793"/AN OR
                "127:293040"/AN OR "128:101936"/AN OR "129:189151"/AN OR
                "131:199535"/AN OR "131:286299"/AN OR "131:31819"/AN OR
                "131:31829"/AN OR "131:351125"/AN OR "132:49832"/AN OR
                "1997:206419"/AN OR "1997:430309"/AN OR "1997:665094"/AN OR
                "1997:787450"/AN OR "1998:378435"/AN OR "1999:176999"/AN OR
                "1999:372044"/AN OR "1999:383492"/AN OR "1999:444724"/AN OR
                "1999:606636"/AN OR "1999:819379"/AN)
L79          11 SEA ABB=ON  PLU=ON  L78 AND L43
L80          16 SEA ABB=ON  PLU=ON  L79 OR L52
L81           1 SEA ABB=ON  PLU=ON  L80 AND L73
L82           1 SEA ABB=ON  PLU=ON  L80 AND L74
L83          27 SEA ABB=ON  PLU=ON  L52 OR L79 OR (L81 OR L82) OR L76
L84          15 SEA ABB=ON  PLU=ON  L61 NOT L63
                D FHIT 7
L85          59 SEA ABB=ON  PLU=ON  L43 (L) 1/NS
L86          45 SEA ABB=ON  PLU=ON  L43 (L) 2/NS
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L87          37 SEA ABB=ON  PLU=ON  L43 (L) 3/NS
L88          31 SEA ABB=ON  PLU=ON  L43 (L) 4/NS
L89          21 SEA ABB=ON  PLU=ON  L43 (L) 5/NS
L90          28 SEA ABB=ON  PLU=ON  L85 NOT L88

    FILE 'CAPLUS' ENTERED AT 12:09:08 ON 11 OCT 2007
L91          80 SEA ABB=ON  PLU=ON  KLAR U?/AU
L92         116 SEA ABB=ON  PLU=ON  BUCHMANN B?/AU
L93          60 SEA ABB=ON  PLU=ON  SCHWEDE W?/AU
L94         186 SEA ABB=ON  PLU=ON  SKUBALLA W?/AU
L95          32 SEA ABB=ON  PLU=ON  L91 AND (L92 OR L93 OR L94)
L96          68 SEA ABB=ON  PLU=ON  L92 AND (L93 OR L94)
L97          24 SEA ABB=ON  PLU=ON  L93 AND L94
L98          25 SEA ABB=ON  PLU=ON  L95 AND (L96 OR L97)
L99          24 SEA ABB=ON  PLU=ON  L96 AND L97
L100         24 SEA ABB=ON  PLU=ON  L98 AND L99
L101          1 SEA ABB=ON  PLU=ON  L100 AND L43

    FILE 'REGISTRY' ENTERED AT 12:11:27 ON 11 OCT 2007

    FILE 'CAPLUS' ENTERED AT 12:11:29 ON 11 OCT 2007
                D STAT QUE L100
                D IBIB ABS L100 1-24
                D IBIB ABS L100 8-24
L102         24 SEA ABB=ON  PLU=ON  L91 AND L92 AND L93 AND L94
                D COST FULL
                D IBIB ABS L102 TOT
                D IBIB L102 10
                D IBIB L102 9
                D ABS L102 8
                D ABS L102 8
                D IBIB ABS L102 9-24

    FILE 'REGISTRY' ENTERED AT 12:16:30 ON 11 OCT 2007

    FILE 'CASREACT' ENTERED AT 12:16:34 ON 11 OCT 2007
                D STAT QUE L33
                D IBIB ABS FHIT L33 1-23

    FILE 'CASREACT' ENTERED AT 12:18:14 ON 11 OCT 2007
                D STAT QUE L90
                D IBIB ABS FHIT L90 1-28
L103          3 SEA ABB=ON  PLU=ON  L77 NOT L90
L104          3 SEA ABB=ON  PLU=ON  L78 NOT L90

    FILE 'CAPLUS' ENTERED AT 12:40:57 ON 11 OCT 2007
L105         21 SEA ABB=ON  PLU=ON  L45 AND PY<2001
                SEL AN

    FILE 'CASREACT' ENTERED AT 12:41:26 ON 11 OCT 2007
L106         21 SEA ABB=ON  PLU=ON  ("126:251010"/AN OR "127:108793"/AN OR
                "127:293040"/AN OR "128:101936"/AN OR "129:189151"/AN OR
                "131:199535"/AN OR "131:286299"/AN OR "131:31819"/AN OR
                "131:31829"/AN OR "131:351125"/AN OR "132:251011"/AN OR
                "132:49832"/AN OR "133:266631"/AN OR "133:266634"/AN OR
                "133:321737"/AN OR "133:362657"/AN OR "134:178371"/AN OR
                "134:29228"/AN OR "134:4795"/AN OR "134:56502"/AN OR "135:37156
                6"/AN OR "1997:206419"/AN OR "1997:430309"/AN OR "1997:665094"/
                AN OR "1997:787450"/AN OR "1998:378435"/AN OR "1999:176999"/AN
                OR "1999:372044"/AN OR "1999:383492"/AN OR "1999:444724"/AN OR
```

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              "1999:606636"/AN OR "1999:819379"/AN OR "2000:514132"/AN OR
              "2000:52387"/AN OR "2000:597944"/AN OR "2000:624043"/AN OR
              "2000:701228"/AN OR "2000:719579"/AN OR "2000:733774"/AN OR
              "2000:842116"/AN OR "2000:853645"/AN OR "2001:843887"/AN)
L107          7 SEA ABB=ON  PLU=ON  L106 NOT L90
L108         21 SEA ABB=ON  PLU=ON  L106 AND L43
L109          7 SEA ABB=ON  PLU=ON  L108 NOT L90
              D STAT QUE L109
              D IBIB ABS FHIT L109 1-7

    FILE HOME

    FILE REGISTRY
    Property values tagged with IC are from the ZIC/VINITI data file
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    STRUCTURE FILE UPDATES:   10 OCT 2007  HIGHEST RN 950149-06-1
    DICTIONARY FILE UPDATES:  10 OCT 2007  HIGHEST RN 950149-06-1

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